PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Uterine balloon tamponade as an adjunct to misoprostol for the treatment of uncontrolled post-partum haemorrhage: a randomized controlled trial in Benin and Mali
AUTHORS	Dumont, Alexandre; BODIN, CECILE; Hounkpatin, Benjamin; Popowski, Thomas; Traoré, Mamadou; Perrin, René; rozenberg, patrick

VERSION 1 - REVIEW

REVIEWER	G Justus Hofmeyr University of the Witwatersrand, Fort Hare, Walter Sisulu, Eastern Cape Department of Health, South Africa
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	This study is of great importance because it is the first randomized trial to assess the effectiveness of UBT. Although the study is underpowered, the findings are in stark contrast to the claims of effectiveness based on observational studies. UBT has been introduced extensively in many countries despite lack of robust evidence of effectiveness. This paper raises the possibility that UBT may be ineffective or even harmful, and highlights the importance of establishing effectiveness before implementing new technologies, and thus the need for larger randomized trials. The paper will need editing to improve the language use. It would be very useful to readers if the authors could give additional information regarding the possible association of high dose misoprostol with the maternal deaths reported, with a reference to the systematic review finding of a trend to increased deaths among women randomly allocated to receive misoprostol in dosages of 600mcg or more (Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organisation 2009; 87: 666-77). If the data are available it would be useful to know for each of the maternal deaths: - Total dose and route of misoprostol - highest temperature recorded - Whether pyrexia or shivering were noted.

REVIEWER	Andrew Weeks University of Liverpool UK ADW is a Scientific Advisor to Azante A/S, a Danish pharmaceutical company. The company pays the University of Liverpool for his time and he receives no personal payments. He is also the inventor of the PPH Butterfly, a device to facilitate uterine compression as part of the management of PPH. The patent is held by the University of Liverpool, but he would receive a share of any future royalties.
REVIEW RETURNED	18-Mar-2017

GENERAL COMMENTS	This is a rare and important study. Conducting any randomised trial in PPH is very difficult - and so to do this in a low resource setting with severe cases of PPH is very impressive indeed. And yet RCTs in PPH are very important due to the tendency for post-partum bleeding to settle spontaneously even with no treatment. Thus every new treatment is initially shown to be 80-90% effective at stopping PPH, even if it it subsequently shown to be of little benefit. This is the case for misoprostol which was initially thought to be of major benefit but which is now known to be of little benefit. The results of this study are important and should help to guide future care. Unfortunately the manuscript is not well written and the analysis suspect. It therefore needs major revision - but then it should be published, perhaps even in the main BMJ so as to gain it more exposure. MAJOR COMMENTS 1. There is considerable bias in the reporting of the study. The authors clearly come from the position that the tamponade device actually works and so all the results and conclusions are written from that perspective - e.g. "we could not confirm the dramatic effect of uterine tamponade", "the results do not exclude a clinically important effect", "the number of patients included... was finally too small to show a significant reduction in the primary outcome", etc, etc. Indeed the last statement is especially odd given that the point estimate is for an increase in the primary outcome and so with greater numbers the authors were likely to show a significant increase in the primary outcome. And that the blood loss of over 1000mls was significantly increased in the balloon group - but this is not mentioned in the discussion or abstract. The discussion and conclusion then do not discuss why the intervention could increase the primary outcome - instead they focus on the study limitations and their belief that the misiprostol was highly effective. It would be far more informative to try and understand why the balloon tamponade did not reduce - or even increased - mortality and morbidity, Reasons for this could be delays, genital tract trauma, belief that the woman was 'sorted' and so not monitored so carefully, or misdiagnosis of atony. The discussion could also discuss why there is such a well trodden path of treatments showing dramatic effects in observational studies which subsequently prove to be ineffective in RCTs. An interesting EBM exercise would be to reverse the results in the two arms and re-interpret. My guess is that the authors would have no doubt that the balloon was superior with a halving of the rate of primary outcome and significantly less blood loss. And it would have been submitted to a higher ranking journal! But the results are

	unexpected and do not support the preconceived opinion - and so they are belittled and treated with suspiscion and derision. 2. This was a study of the use of uterine tamponade plus misoprostol versus misoprostol alone. As misoprostol was used in both arms it is impossible to say whether the misoprostol is effective or not. To suggest, on the basis of the 'high success rate' that misoprostol is effective as a second line treatment seems odd. Indeed, the Widmer study is one of the biggest studies ever of PPH treatment and compared misoprostol to placebo as an adjunct to oxytocin for the treatment of atonic PPH in 1000 women (Widmer M et al; Lancet 2010). There was no difference at all between the groups in outcomes - not even a hint of benefit. As it was being used alongside oxytocin as first line treatment, it is very similar in practice to a second line treatment (as the sublingual misoprostol lasts many hours) - the only difference being that it would be a smaller group of more resistant cases that would be in a second line study. So i think that the authors are a little harsh to say that "there is no randomised controlled trial to test the efficacy of misoprostol as a second line therapy" and that there is "limited data regarding efficacy". Indeed, most of those who have access to oxytocin have now stopped using misoprostol for PPH treatment on the basis of that study. 3. One likely difference between the groups was the delay to treatment following randomisation. Many timings are given - but not the time from randomisation to balloon insertion. Already the time to giving the misoprostol is delayed in the balloon arm (only 46% within 30 mins compared to 63% in the miso only arm), and i suspect that the time to insertion of the balloon is also delayed. In the first 30 minutes following failure of first line therapy, many women will stop bleeding spontaneously. It is unclear from the text how often this happened or what happened to women who had stopped bleeding. Did they still receive treatment including balloon insertion, or were they just observed? My guess is that they were not included. But that means that those still bleeding at the time of balloon insertion must have been in a very bad condition indeed - and would be very difficult to save. Alternatively, the clinicians may have attempted to insert a balloon into women who had stopped bleeding already - this would be difficult and potentially even cause trauma and provoke more bleeding. Both these scenarios could explain the disparity in the results between the two groups. But the authors need to be explicit about what happened between randomisation and treatment, what length of time that was, and how many stopped bleeding before balloon insertion. MINOR COMMENTS In the methods section: 1. was was AMTSL 'presumably systematically performed"? 2. it is unclear what happened with retained placentas. Were they excluded? Or, if included, how was the balloon inserted? Was there manual removal and then insertion? The method for dealing with this should be included. There is data in table 2 - but it is unclear whether all these were after randomisation, or also before. 3. How long was oxytocin given before deciding that it had not worked? What were the criteria? 4. The exact chronology needs to be made explicit at the time of randomisation - who randomised? Then who made up the balloon catheter? Who gave the misoprostol? Was this done in theatre or on the wards? Was the cavity explored manually first to exclude retained products of conception? Was the balloon inserted under

	GA, or manually on the delivery suite? Using hands only or via a speculum with instruments? Where were the compresses placed? The authors say 'vaginal fornix' but that is a very small part of the vagina - presumably it is a large gauze pack placed in the vagina? 5. Was the blood loss estimated or measured? 6. Were the case report forms on paper and then entered (double?) by researchers onto a computer database? 7. How was the allocation concealed? Was it sealed opaque numbered envelopes? 8. 'Qualitative data' should read 'dichotomous data' Results 1. The outcomes are worse across the board in the balloon group. But there are no details of the results from the 15 day follow-up telephone call. This should be added to the CONSORT flow chart as well as the results. 2. There are errors in the results in tables 1 and 2, and this makes me concerned about the rest of the data that i cannot verify. E.g. multiple pregnancy 4/59 is not 10% and the percentages for manual removal and tranexamic acid are also wrong in table 2.

REVIEWER	A. Metin Gülmezoglu World Health Organization, Switzerland
REVIEW RETURNED	24-Mar-2017

GENERAL COMMENTS	First of all the authors should be congratulated for conducting the first randomized controlled trial of balloon tamponade. In doing that the authors also managed to have a ethically acceptable control group. Balloon tamponade slowly entered into clinical practice without having been subjected to rigorous research. This was partly due to some expert users having impressive clinical experience with its use. At the same time, its use varies across facilities, countries and regions globally. This trial is timely because there has been a general move towards acceptance of balloon tamponade as an effective treatment for PPH and this trial results should put the brakes on for moving into this treatment as an already-proven treatment. The trial has several strengths and weaknesses and the authors have highlighted some of them. 1. Patient population is appropriate. Although it could be argued that in general, balloon tamponade should be indicated after additional uterotonics have failed and, it does not seem to be an entry criterion in the trial, the fact that diagnosis and treatment were often delayed and two patients having died while waiting for the intervention suggests that the population was fairly high risk. 2. The use of the condom catheter and misoprostol for control seem appropriate. Rectal misoprostol is generally not recommended due to its unknown absorption kinetics but it is probably in the local protocols. 3. Outcomes are also appropriate for the design. 4. DESIGN: It seems that women received prophylactic oxytocin, then therapeutic oxytocin (at various doses) and after that if the bleeding continued after 20 minutes and was thought to be due to atony the women were randomized. The treatment was considered successful if it was controlled within 15 minutes of the intervention. I think the sequence of events from eligibility assessment to randomization and outcomes could be described more clearly.

	Of course, the trial intervention could not be blinded and that puts all subjective outcomes in a difficult to interpret category. The fact that the main trial outcomes are 'hard' outcomes makes interpretation easier though. 5. SAMPLE SIZE: The authors estimated an effect size of 75% relative reduction (19% absolute reduction) and based it on 25% baseline event rate. The baseline event rate turned out to be 7% at the end of the trial which obviously has an impact on the power. 6. INTERPRETATION: As expected but not loudly expressed to date, the success rates from case series and reports seem to be exaggerated. There is further information from France to support this which is a generally known phenomenon i.e. publication bias. It is clear that some women have dangerously profuse haemorrhage that makes any intervention difficult to succeed while others may bleed more slowly and some may stop bleeding spontaneously. The trial being underpowered makes it somewhat difficult to interpret the 87% and 93% success rates because the condom group also received misoprostol. It could be argued that commercial tamponade devices are more effective (but there is no evidence for that either) or that the devices were slow and too late to be inserted that affected the success rates. What is clear is, that the dramatic effects of condom tamponade have not been confirmed in this first RCT. 7. It is clear that the settings in which the trial was conducted is appropriate for use of additional interventions such as balloon tamponade. The findings make it now imperative that larger trials of balloon tamponade be undertaken in these settings.

REVIEWER	Alouini, S. Regional Hospital Center of Orléans, FRANCE
REVIEW RETURNED	24-Mar-2017

GENERAL COMMENTS	Cecile Bodin and coauthors evaluated low cost uterine balloon tamponade with condom-catheter device to stop post-partum hemorrhage PPH in two African countries: Benin and Mali. The authors compared two groups receiving second line therapy with and without condom-catheter device insertion. Both groups had an adjunction of misoprostol. Introduction Some references on the use of condom uterine balloon tamponade should be cited: For example: Darvish et al. Bakri balloon versus condom-loaded Foley's catheter for treatment of atonic postpartum hemorrhage secondary to vaginal delivery: a randomized controlled trial. J Matern Fetal Neonatal Med. 2017 Aderoba AK et al. Condom-catheter tamponade for the treatment of postpartum haemorrhage and factors associated with success: a prospective observational study. BJOG. 2016 Mvundura M et al. Cost-effectiveness of condom uterine balloon tamponade to control severe postpartum hemorrhage in Kenya. Int J Gynaecol Obstet. 2017 Methods PPH was defined as: “total blood loss more than 1000 mL” Usually PPH is defined by blood loss more than 500 ml. Visual estimation of blood loss was used to quantify the volume of blood loss. It is a subjective criterion and could not be used as

	quantitative criteria. Other criteria should be added like clinical criteria (tachycardia, drop of arterial blood pressure…) transfusion of blood products, number, hematocrit, hemoglobin, red count cells… Results as there is no quantitative evaluation of blood loss with a collector bag this result should be modified: “An increased proportion of women with tamponade and misoprostol versus misoprostol alone have lost more than 1000 mL of blood as estimated on the basis of the health provider’s clinical judgment (relative risk 1.52 ; 95% confidence interval 1.15 to 2.00, p-value < 0.01) “ The visual evaluation of volume of blood loss is subjective and statistics are difficult to apply. Misoprostol was used in the two groups therefore it is difficult to conclude that misoprostol had a significant impact to stop PPH. Discussion In this study Condom-catheter tamponade was inefficient to control PPH, however other recent studies showed that condom UBT was efficient to control PPH (see references in Introduction). How the authors explain these differences? The number of patients who died is very high. Is the insertion of condoms was responsible of a delay to perform laparotomy? Why more women died in the group tamponade + misoprostol (6 versus 1 in the misoprostol group alone) , it should be explained ? The authors should include a paragraph how to improve the management of PPH: What are the criteria of early and objective diagnosis of PPH. A collector bag is not very expansive but useful to evaluate more objectively blood loss. Timing of tamponade balloon insertion and more invasive technics such as hemostatic sutures, vessel ligations and hysterectomies should be defined.. Surgical technique like hemostatic sutures or vessels ligations should be applied more quickly.

REVIEWER	Akmal El-Mazny Cairo University, Egypt
REVIEW RETURNED	15-Apr-2017

GENERAL COMMENTS	Thank you for giving me the opportunity to review this interesting study "Uterine balloon tamponade as an adjunct to misoprostol for the treatment of uncontrolled post-partum haemorrhage: a randomized controlled trial in Benin and Mali". However, I have some comments and recommendations: Abstract: - Include key data. Introduction: - Emphasize the gap of knowledge. Methods: - Adequately describe inclusion and exclusion criteria. - Mention appropriate details of techniques. - Add important relevant references. - Emphasize the effect size. Results: - Do not duplicate, the text should complement the tables and

	figures. - Clarify the effect size for the main outcome. - Specify exact p values. Discussion: - Justify the differences from other studies. - Suggest clinical implications. References: - Stick to the format of the journal.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 : G Justus Hofmeyr (JH)

JH : This study is of great importance because it is the first randomized trial to assess the effectiveness of UBT. Although the study is underpowered, the findings are in stark contrast to the claims of effectiveness based on observational studies. UBT has been introduced extensively in many countries despite lack of robust evidence of effectiveness. This paper raises the possibility that UBT may be ineffective or even harmful, and highlights the importance of establishing effectiveness before implementing new technologies, and thus the need for larger randomized trials.

JH : The paper will need editing to improve the language use.

Answer : We thank prof. Hofmeyr for indicating the need to improve the language use. The new version of the manuscript has been reviewed by an english spoken person.

JH : It would be very useful to readers if the authors could give additional information regarding the possible association of high dose misoprostol with the maternal deaths reported, with a reference to the systematic review finding of a trend to increased deaths among women randomly allocated to receive misoprostol in dosages of 600mcg or more (Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organisation 2009; 87: 666-77). If the data are available it would be useful to know for each of the maternal deaths: Total dose and route of misoprostol-highest temperature recorded- Whether pyrexia or shivering were noted.

Answer : We thank the Prof. Hofmeyr for pointing out the potential deleterious effect of misoprostol in this trial. We agree it is useful to know for each of the maternal deaths the total dose and route of misoprostol administration and reported side effects. Among the seven registered maternal deaths, two women from the experimental group did not receive allocated intervention (misoprostol + tamponade). In one case, the woman died from a massive haemorrhage within 20 minutes after randomization and before that misoprostol could be administered. In the other case, considering the severity of the bleedings, the staff decided to postpone the administration of misoprostol and a laparotomy was realized just after randomization. Among the four deceased women, who effectively received misoprostol, in the experimental group (misoprostol + tamponade), there was two cases in which misoprostol was administrated with the total dose of 1400 µg (400 µg intravaginal for labor induction and 1000 µg intrarectal for PPH treatment). For the third deceased women, intra-rectal misoprostol was administered with the total dose of 1000 µg. For the last case, misoprostol was administered under the tongue with the total dose of 600 µg. For the maternal death from the control group, misoprostol was administrated in the rectum with the total dose of 1000 µg. We have modified the last paragraph of the “Results” section to make it more explicit. Please, see the changes to our revised manuscript. Moreover, we added the following paragraph in the discussion section.

“On the other hand, our results could point out the potential deleterious effect of high dose of misoprostol. 21 Indeed, five of the seven registered maternal death in this trial could be associated with high dose misoprostol (600 µg and more), considering the results of the systematic review of Hofmeyer and colleagues published in the Bulletin of the World Health Organization. However, among these five women who died after the administration of misoprostol, no known side effects of the misoprostol as pyrexia or shiving, was reported by clinicians. For this reason, it is not clear to attribute these deaths to the misoprostol.”

Reviewer 2 : Andrew Weeks

AW : This is a rare and important study. Conducting any randomised trial in PPH is very difficult - and so to do this in a low resource setting with severe cases of PPH is very impressive indeed. And yet RCTs in PPH are very important due to the tendency for post-partum bleeding to settle spontaneously even with no treatment. Thus every new treatment is initially shown to be 80-90% effective at stopping PPH, even if it it subsequently shown to be of little benefit. This is the case for misoprostol which was initially thought to be of major benefit but which is now known to be of little benefit.

The results of this study are important and should help to guide future care. Unfortunately the manuscript is not well written and the analysis suspect. It therefore needs major revision - but then it should be published, perhaps even in the main BMJ so as to gain it more exposure.

MAJOR COMMENTS

1. There is considerable bias in the reporting of the study. The authors clearly come from the position that the tamponade device actually works and so all the results and conclusions are written from that perspective - e.g. "we could not confirm the dramatic effect of uterine tamponade", "the results do not exclude a clinically important effect", "the number of patients included... was finally too small to show a significant reduction in the primary outcome", etc, etc. Indeed the last statement is especially odd given that the point estimate is for an increase in the primary outcome and so with greater numbers the authors were likely to show a significant increase in the primary outcome. And that the blood loss of over 1000mls was significantly increased in the balloon group - but this is not mentioned in the discussion or abstract. The discussion and conclusion then do not discuss why the intervention could increase the primary outcome - instead they focus on the study limitations and their belief that the misiprostol was highly effective. It would be far more informative to try and understand why the balloon tamponade did not reduce - or even increased - mortality and morbidity, Reasons for this could be delays, genital tract trauma, belief that the woman was 'sorted' and so not monitored so carefully, or misdiagnosis of atony. The discussion could also discuss why there is such a well trodden path of treatments showing dramatic effects in observational studies which subsequently prove to be ineffective in RCTs.
An interesting EBM exercise would be to reverse the results in the two arms and re-interpret. My guess is that the authors would have no doubt that the balloon was superior with a halving of the rate of primary outcome and significantly less blood loss. And it would have been submitted to a higher ranking journal! But the results are unexpected and do not support the preconceived opinion - and so they are belittled and treated with suspiscion and derision.

Answer : Indeed, we were very surprised by the results of our trial. Regarding the systematic review of Tindell and colleagues (Tindell K, Garfinkel R, Abu-Haydar E, et al. Uterine balloon tamponade for the treatment of postpartum haemorrhage in resource-poor settings: a systematic review. BJOG 2012;DOI: 10.1111/j.1471-0528.2012.03454.x), we expected that tamponade and misoprostol was

more effective than misoprostol alone. However, we tested the difference in the primary outcome between the two groups in bilateral formulation, making no specific assumption about the direction of this difference. The calculation of the sample size was based on a bilateral formulation too.
We thank the Reviewer for indicating the need to discuss more in detail the reason why the balloon tamponade did not reduce - or even increased – maternal mortality and morbidity. Following the Reviewer's recommendation, we modified the "Discussion" section to make it more explicit. Delays in PPH management may explain increased maternal morbidity in the tamponade and misoprostol group. We added the following text at the end of the first paragraph of the discussion « Strengths and weaknesses of the study » :
"Otherwise, delays in the second-line PPH management could explain the significantly increased blood loss over 1000 mL and the higher case-fatality rate in the misoprostol and tamponade group compared to the control group. Indeed, delay in the administration of misoprostol was more frequent in the experimental group (Table 2). Moreover, the condom catheter was inserted 30 minutes and more after the diagnosis of PPH in 42% of the cases (Table 2), despite our efforts in order to improve the availability of the different components of the UBT device. Among the four women who died after the uterine balloon tamponade, no hysterectomy was performed in three cases while UBT device failed to stop the bleedings. Although this was not reported by both maternal death reviewers, the uterine balloon tamponade may have delayed the decision to perform a hysterectomy. Finally, in the referal hospitals, a large part of the uterine balloon tamponade and misoprostol was administered by the doctors to the operating theatre. However, the recurring unavailability of the theatre had an important consequence in the delays for the experimental group. In the control group (misoprostol only), the misoprostol was always administered in delivery room."

The conclusion of the revised manuscript and abstract was modified too, and it now reads as follows:

"In low resource settings and urban context, where operating theatres are available, the use of condom-catheter UBT in addition to misoprostol has no significant effect on recourse to invasive surgery. However, delays in post-partum haemorrhage management may explain increased maternal morbidity and mortality among women treated with tamponade and misoprostol. Further studies are needed to ascertain optimal approaches for the medical management of patients with uterine atony unresponsive to oxytocin."

2. This was a study of the use of uterine tamponade plus misoprostol versus misoprostol alone. As misoprostol was used in both arms it is impossible to say whether the misoprostol is effective or not. To suggest, on the basis of the 'high success rate' that misoprostol is effective as a second line treatment seems odd. Indeed, the Widmer study is one of the biggest studies ever of PPH treatment and compared misoprostol to placebo as an adjunct to oxytocin for the treatment of atonic PPH in 1000 women (Widmer M et al; Lancet 2010). There was no difference at all between the groups in outcomes - not even a hint of benefit. As it was being used alongside oxytocin as first line treatment, it is very similar in practice to a second line treatment (as the sublingual misoprostol lasts many hours) - the only difference being that it would be a smaller group of more resistant cases that would be in a second line study. So i think that the authors are a little harsh to say that "there is no randomised controlled trial to test the efficacy of misoprostol as a second line therapy" and that there is "limited data regarding efficacy". Indeed, most of those who have access to oxytocin have now stopped using misoprostol for PPH treatment on the basis of that study.

Answer : We agree that our data did not support our conclusion about the possible effect of misoprostol in second-line PPH treatment. We have modified the conclusion as presented above and the discussion as follows :

"20 If there is evidence that the misoprostol provides no added benefit when it is given simultaneously with other injectable uterotonics drugs for the first-line treatment of PPH, 21 there is no randomized

controlled trial in order to test the efficacy of the misoprostol as a second line therapy."

3. One likely difference between the groups was the delay to treatment following randomisation. Many timings are given - but not the time from randomisation to balloon insertion. Already the time to giving the misoprostol is delayed in the balloon arm (only 46% within 30 mins compared to 63% in the miso only arm), and i suspect that the time to insertion of the balloon is also delayed. In the first 30 minutes following failure of first line therapy, many women will stop bleeding spontaneously. It is unclear from the text how often this happened or what happened to women who had stopped bleeding. Did they still receive treatment including balloon insertion, or were they just observed? My guess is that they were not included. But that means that those still bleeding at the time of balloon insertion must have been in a very bad condition indeed - and would be very difficult to save. Alternatively, the clinicians may have attempted to insert a balloon into women who had stopped bleeding already - this would be difficult and potentially even cause trauma and provoke more bleeding. Both these scenarios could explain the disparity in the results between the two groups. But the authors need to be explicit about what happened between randomisation and treatment, what length of time that was, and how many stopped bleeding before balloon insertion.

Answer : We thank the Reviewer for pointing out the need to present more in detail the delay to treatment following the randomization. We added one line in Table 2 to present delay in balloon As presented in this table, 58% of women had uterine balloon tamponade in the first 30 minutes following PPH diagnosis.
Unfortunately, information was missing about women who stopped bleeding spontaneously in the first 30 minutes following failure of first line therapy However, these women were included in the intention-to-treat analysis, as stated in the original protocol of our trial (http://www.controlled-trials.com/ISRCTN01202389). Among 57 patients allocated to the misoprostol and tamponade arm, two women did not receive the condom-catheter because they died before the procedure and two women did not benefit the tamponade because staff decided to postpone the treatment for unknown reasons. For these two women who survived, it is likely that the condom catheter was not inserted because the woman stopped bleeding spontaneously. However, it is unlikely that clinicians attempted to insert a balloon into women who had stopped bleeding spontaneously.

MINOR COMMENTS

In the methods section:

1. What was AMTSL "presumably systematically performed"?

Answer : « AMTSL 'presumably systematically performed » means that AMTSL was supposed to be performed for all patients who delivered in participating centers and that we assume that this was not the case for some of patients. As shown in Table 1, Three women in the experimental group and four women in the control group had no received preventive oxytocin.

2. it is unclear what happened with retained placentas. Were they excluded? Or, if included, how was the balloon inserted? Was there manual removal and then insertion? The method for dealing with this should be included. There is data in table 2 - but it is unclear whether all these were after randomisation, or also before.

Answer : women with retained placenta were not excluded. The condom catheter was inserted after manual removal of the placenta. Following the Reviewer's commendation, we included this information in the Method section.

3. How long was oxytocin given before deciding that it had not worked? What were the criteria?

Answer : as stated in the Method section, PPH was defined as uncontrolled if active bleeds did not cease within 20 minutes of initial treatment with oxytocin, according to the visual estimation of blood loss and patient status by the caregiver.

4. The exact chronology needs to be made explicit at the time of randomisation who randomised? Then who made up the balloon catheter? Who gave the misoprostol? Was this done in theatre or on the wards? Was the cavity explored manually first to exclude retained products of conception? Was the balloon inserted under GA, or manually on the delivery suite? Using hands only or via a speculum with instruments? Where were the compresses placed? The authors say 'vaginal fornix' but that is a very small part of the vagina – presumably it is a large gauze pack placed in the vagina?

Answer : We thank the Reviewer for indicating the need to clarify the method used for randomization. We have expanded the original text. The revised paragraph « randomization » now reads as follows :

“The trial supervisor was called by phone by the caregiver (a midwife or a doctor) and he checked with her or him the inclusion and exclusion criteria. If the patient was eligible for the trial, she was randomized using the computer-generated randomization sequence. If the patient was allocated in the tamponade and misoprostol group, the caregiver inserted the balloon catheter in theater or on the wards, depending on the context. The uterine cavity was explored manually first to exclude retained products of conception. The condom catheter was inserted manually on the delivery suite using hands only. Then the compresses were placed at the bottom of vagina, in contact with the cervix and the balloon.”

5. Was the blood loss estimated or measured?

Answer : Since the use of collection bag is not a common practice in Benin and Mali, PPH was clinically assessed by the caregivers (midwife or doctor) according to the visual estimation of excessive blood loss and patient status (blood pressure and cardiac frequency).

6. Were the case report forms on paper and then entered (double?) by researchers onto a computer database ?

Answer : Case report forms on paper were regularly controlled for data quality and entered using double data entry by researchers onto a computer database.

7. How was the allocation concealed? Was it sealed opaque numbered envelopes?

Answer : The computer-generated randomization sequence was only known by the principal investigator (AD), the project manager (CB) and both local trial supervisors in Benin and Mali who were not involved in patients care. We did not use sealed opaque numbered envelopes. The four previously referred people were in possession of a list indicating, by center, the treatment to be assigned to every new randomized patient

8. 'Qualitative data' should read 'dichotomous data'

Answer : Thank you. Changes has been made as proposed

Results

1. The outcomes are worse across the board in the balloon group. But there are no details of the

results from the 15 day follow-up telephone call. This should be added to the CONSORT flow chart as well as the results.

Answer : as stated in the original manuscript, women were called by phone within 15 days after hospital discharge to get information about the post-partum period at home and adverse events. No patients were lost from the randomization to the final follow up by phone, except seven women who died before hospital discharge (6 women in the experimental arm and 1 woman in the control arm). For the 109 remaining women, no problem or side effects in the post-partum period were reported. As recommended by the Reviewer, this information was added in the CONSORT Flow Chart (Figure 1) and in the « results » :

2. There are errors in the results in tables 1 and 2, and this makes me concerned about the rest of the data that i cannot verify. E.g. multiple pregnancy 4/59 is not 10% and the percentages for manual removal and tranexamic acid are also wrong in table 2.

Answer : Thank you for pointing out these errrors which were corrected. We checked carefully other results in tables 1, 2 and 3. There were not other errors.

Reviewer 3 : A. Metin Gülmezoglu

First of all the authors should be congratulated for conducting the first randomized controlled trial of balloon tamponade. In doing that the authors also managed to have a ethically acceptable control group. Balloon tamponade slowly entered into clinical practice without having been subjected to rigorous research. This was partly due to some expert users having impressive clinical experience with its use. At the same time, its use varies across facilities, countries and regions globally. This trial is timely because there has been a general move towards acceptance of balloon tamponade as an effective treatment for PPH and this trial results should put the brakes on for moving into this treatment as an already-proven treatment.

The trial has several strengths and weaknesses and the authors have highlighted some of them.

1. Patient population is appropriate. Although it could be argued that in general, balloon tamponade should be indicated after additional uterotonics have failed and, it does not seem to be an entry criterion in the trial, the fact that diagnosis and treatment were often delayed and two patients having died while waiting for the intervention suggests that the population was fairly high risk.

Answer : We thank the Reviewer for pointing out this potential ambiguity. Indeed, women delivering vaginally who had clinically diagnosed post-partum haemorrhage that was suspected to be due to uterine atony and not responsive to first-line oxytocin were enrolled. In the experimental group, we decided to use balloon tamponade and misoprostol in the same time because we wished to avoid delays in second-line PPH management. Despite this decision, treatment was often delayed for multiple reasons. As discussed above with Reviewer 2, uterine balloon tamponade may have delayed the decision to perform a hysterectomy.

2. The use of the condom catheter and misoprostol for control seem appropriate. Rectal misoprostol is generally not recommended due to its unknown absorption kinetics but it is probably in the local protocols.

Answer : Yes, we tried to be as close as possible to local clinical guidelines. For this reason, we

considered two routes of misoprostol administration : intra-rectal and sublingual. The route of administration recommended for the misoprostol was the sublingual way (600 µg of misoprostol).

3. Outcomes are also appropriate for the design.

Answer : Thank you

4. DESIGN: It seems that women received prophylactic oxytocin, then therapeutic oxytocin (at various doses) and after that if the bleeding continued after 20 minutes and was thought to be due to atony the women were randomized. The treatment was considered successful if it was controlled within 15 minutes of the intervention. I think the sequence of events from eligibility assessment to randomization and outcomes could be described more clearly.

Answer : We thank the Reviewer to point out the need to clarify the sequence of events from eligibility assessment. We added the following paragraph in the 'Intervention' section as follows:

The sequence of events, from eligibility assessment, can be summarized as follows: if the bleedings continued 20 minutes after the administration of first-line treatment by oxytocin, the woman was randomized, the misoprostol administered and the condom catheter inserted, according to group allocation. The treatment was considered as successful if the bleedings were controlled within 15 minutes after the intervention. If the bleeding was not controlled within 15 minutes, immediate surgery was recommended.

Of course, the trial intervention could not be blinded and that puts all subjective outcomes in a difficult to interpret category. The fact that the main trial outcomes are 'hard' outcomes makes interpretation easier though.

Answer : We think so

5. SAMPLE SIZE: The authors estimated an effect size of 75% relative reduction (19% absolute reduction) and based it on 25% baseline event rate. The baseline event rate turned out to be 7% at the end of the trial which obviously has an impact on the power.

Answer : We agree. For this reason, the study was underpowered as mentioned in the section "discussion":
« However, the present trial does not exclude the possibility that misoprostol could be effective in the treatment of uterine atony unresponsive to oxytocin. Indeed, the bleeds were controlled by misoprostol in 93% of women in our trial. This success rate is higher than that reported in previous descriptive studies (between 63% and 87%)". References 6 and 7.

6. INTERPRETATION: As expected but not loudly expressed to date, the success rates from case series and reports seem to be exaggerated. There is further information from France to support this which is a generally known phenomenon i.e. publication bias. It is clear that some women have dangerously profuse haemorrhage that makes any intervention difficult to succeed while others may bleed more slowly and some may stop bleeding spontaneously. The trial being underpowered makes it somewhat difficult to interpret the 87% and 93% success rates because the condom group also received misoprostol. It could be argued that commercial tamponade devices are more effective (but there is no evidence for that either) or that the devices were slow and too late to be inserted that affected the success rates. What is clear is, that the dramatic effects of condom tamponade have not been confirmed in this first RCT.

Answer : We thank Prof. Gülmezoglu for his interpretation of the results. We agree with both proposals. First, the randomized controlled trial of Darwish et al. published online in Mars 2017 showed that condom catheter device is as effective as Bakri balloon but requires a significant bit longer time to stop bleeding. We added this point of discussion and corresponding reference (18). Second, as pointed out also by Reviewer 2, we think that the balloon tamponade may increase the risk of delays in PPH management (please see our detailed answer above)

7. It is clear that the settings in which the trial was conducted is appropriate for use of additional interventions such as balloon tamponade. The findings make it now imperative that larger trials of balloon tamponade be undertaken in these settings.

Answer : We agree. Our conclusion has been changed in this way.

Reviewer: 4 : ALOUINI

Cecile Bodin and coauthors evaluated low cost uterine balloon tamponade with condom-catheter device to stop post-partum hemorrhage PPH in two African countries: Benin and Mali. The authors compared two groups receiving second line therapy with and without condom-catheter device insertion. Both groups had an adjunction of misoprostol.

Introduction : Some references on the use of condom uterine balloon tamponade should be cited. For example:
- Darvish et al. Bakri balloon versus condom-loaded Foley's catheter for treatment of atonic postpartum hemorrhage secondary to vaginal delivery: a randomized controlled trial. J Matern Fetal Neonatal Med. 2017
- Aderoba AK et al. Condom-catheter tamponade for the treatment of postpartum haemorrhage and factors associated with success: a prospective observational study. BJOG. 2016
- Mvundura M et al. Cost-effectiveness of condom uterine balloon tamponade to control severe postpartum hemorrhage in Kenya. Int J Gynaecol Obstet. 2017

Answer : Thank you we take into account two of these references (Darvish & al. and Aderoba & al.). For the last one (Myundura et al.), we think that cost-effectiveness analysis is not relevant for our article, since there is no evidence of the effectiveness of the condom uterine balloon tamponade. Please see discussion section.

Methods : PPH was defined as: “total blood loss more than 1000 mL”. Usually PPH is defined by blood loss more than 500 ml. Visual estimation of blood loss was used to quantify the volume of blood loss. It is a subjective criterion and could not be used as quantitative criteria. Other criteria should be added like clinical criteria (tachycardia, drop of arterial blood pressure…) transfusion of blood products, number, hematocrit, hemoglobin, red count cells…

Answer : Since the use of collection bag is not a common practice in Benin and Mali, PPH was clinically assessed by the caregivers (midwife or doctor) according to the visual estimation of excessive blood loss and patient status (blood pressure and cardiac frequency). We agree that it is a subjective method to estimate blood loss. However, this method was used in both group. Accordingly, it should not affect the results regarding the effectiveness of tamponade and misoprostol versus misoprostol alone. Moreover, we have had discussions with all the investigators regarding collection bag and we decided that it was not relevant to use them in this trial. Indeed, this kind of bag allows

collecting blood but also all the other liquids (physiological fluids, treatments…) which falsify the blood loss estimation.

Results : as there is no quantitative evaluation of blood loss with a collector bag this result should be modified: “An increased proportion of women with tamponade and misoprostol versus misoprostol alone have lost more than 1000 mL of blood as estimated on the basis of the health provider’s clinical judgment (relative risk 1.52 ; 95% confidence interval 1.15 to 2.00, p-value < 0.01) “. The visual evaluation of volume of blood loss is subjective and statistics are difficult to apply.

Answer : Although the estimation of blood loss was subjective, we asked to caregivers whether the volume was superior or inferior to 1000 mL. According to the answers, we could classify blood loss in two categories : (1) 500 mL to 999 mL, and (2) 1000 mL and more. In this situation, statistics was possible to apply if binary outcome was defined (blood loss more than 1000 mL : Yes or No).

Misoprostol was used in the two groups therefore it is difficult to conclude that misoprostol had a significant impact to stop PPH.

Answer : We agree. Reviewer 2 made a similar recommendation. Changes have been made as proposed. Please, see our answer above.

Discussion : In this study Condom-catheter tamponade was inefficient to control PPH, however other recent studies showed that condom UBT was efficient to control PPH (see references in Introduction). How the authors explain these differences?

Answer : The success rates of condom catheter tamponade from case series and reports (Aderoba & al and Tindell & al) seem to be exaggerated and probably due to publication bias (no publication of inconclusive studies). Moreover, in the article from Darwish & al, there is no comparison with the standard treatment (misoprostol). Indeed, it is a comparison between two types of intra-uterine tamponade: the balloon of Bakri and the condom-catheter device. Consequently, there is no evidence of efficiency of the condom-catheter device compared to the standard treatment (misoprostol).

The number of patients who died is very high. Is the insertion of condoms was responsible of a delay to perform laparotomy? Why more women died in the group tamponade + misoprostol (6 versus 1 in the misoprostol group alone) , it should be explained ?

Answer : Yes, we think that uterine balloon tamponade may have delayed the decision to perform a hysterectomy. As we explained to Reviewer 2, this point has been discussed in more detail and changes have been made as follows in the section “discussion / Strengths and weaknesses of the study”:

Otherwise, delays in the second-line PPH management could explain the significantly increased blood loss over 1000 mL and the higher case-fatality rate in the misoprostol and tamponade group as compared with the control group. Indeed, delay in misoprostol administration was more frequent in the experimental group (Table 2). Moreover, the condom catheter was inserted 30 minutes and more after PPH diagnosis in 42% of cases (Table 2), despite our efforts to improve the availability of the different components of the UBT device. Among four women who died after the uterine balloon tamponade, no hysterectomy was performed in three cases while UBT failed to stop the bleeding. Although this was not reported by both maternal death reviewers, uterine balloon tamponade may have delayed the decision to perform a hysterectomy.

The authors should include a paragraph how to improve the management of PPH: What are the criteria of early and objective diagnosis of PPH. A collector bag is not very expansive but useful to evaluate more objectively blood loss. Timing of tamponade balloon insertion and more invasive technics such as hemostatic sutures, vessel ligations and hysterectomies should be defined. Surgical technique like hemostatic sutures or vessels ligations should be applied more quickly.

Answer : we agree that more information is needed to improve the management of PPH. However, the results of this trial do not allow us to make specific recommendations. Further studies are needed to ascertain optimal approaches for managing patients with uterine atony unresponsive to oxytocin.

Reviewer 5 : Akmal El-Mazny (AEM)

AEM : Thank you for giving me the opportunity to review this interesting study "Uterine balloon tamponade as an adjunct to misoprostol for the treatment of uncontrolled post-partum haemorrhage: a randomized controlled trial in Benin and Mali". However, I have some comments and recommendations:

AEM : Abstract: Include key data.

Answer : we have mentionned in the revised abstract the significant increase in blood loss > 1000 mL and marked (but not significant) increase in maternal deaths in the experimental group as compared with the control group.

AEM : Introduction: Emphasize the gap of knowledge.

Answer : We pointed out that misoprostol and uterine balloon tamponade were introduced extensively in many countries despite lack of robust evidence of effectiveness.

AEM : Methods: Adequately describe inclusion and exclusion criteria. Mention appropriate details of techniques. Add important relevant references. Emphasize the effect size.

Answer : We thank the Reviewer to point out the need to clarify some elements of our methodology. Other Reviewers made recommendations in this way. Please, see our answers above and additional information that is now available in the revised manuscrit.

AEM : Results: Do not duplicate, the text should complement the tables and figures. Clarify the effect size for the main outcome. Specify exact p values.

Answer : We have clarified the effcte size and specified exact p-value for each of the primary and secondary outcomes. Please, see the revised table 3.

Discussion: Justify the differences from other studies. Suggest clinical implications.

Answer : we revised the discussion section in this way. Please, see the changes in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	GJ Hofmeyr Effective Care Research Unit Universities of the Witwatersrand, Fort Hare and Walter Sisulu

	South Africa
REVIEW RETURNED	03-Jun-2017

GENERAL COMMENTS	This is an important paper because it is to my knowledge the first randomized trial of uterine ballooon tamponade for PPH. Although underpowered for the primary outcome (death or invasive surgery), the trend to increased primary outcome, increased blood transfusion and to increased death (6 versus 1), and the significant increase in blood loss >1000ml alerts global institutions to the urgent need for further randomized trials. I would suggest 3 minor changes: 1. Background: The authors state that there are no randomized trials of misoprostol for treatment of PPH - perhaps rather refer to the large WHO study (Widmer et al 2010) which is in the paper's reference list Discussion - implications for practice: 2. perhaps add the reference to the WHO Bulletin paper referred to: Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organisation 2009; 87: 666-77 Published online 20 July 2009 3. The statement: "Indeed, the bleedings were controlled by misoprostol in 93% of women in our trial" could perhaps be reworded: "Indeed, the bleeding was controlled in 93% of women in our trial, all of whom received misoprostol. However, as there was no control group who did not receive misoprostol, we cannot be sure in how many cases the bleeding would have ceased without misoprostol".

REVIEWER	Andrew Weeks University of Liverpool, UK
REVIEW RETURNED	15-Jun-2017

GENERAL COMMENTS	The manuscript has improved but there remain many issues both with the content and grammar. 1. The text remains overenthusiastic about uterine tamponade. Examples of this are seen in the tweetable abstract and the limitations sections following the abstract ("The number of patient included, whose calculation was based on published data, was finally too small to show a significant reduction in the primary outcome"). Similar problems are seen elsewhere. 2. The blood loss result in the abstract has no RR and 95% CI. 3. The response states that "PPH was clinically assessed by the caregivers (midwife or doctor) according to the visual estimation of excessive blood loss and patient status (blood pressure and cardiac frequency)" - this should be added to the methods. 4. It is interesting that the methods now suggest that all participants in the balloon tamponade group had manual uterine exploration whereas that was only done for the 10 women in the misoprostol group who required manual removal of placenta. Trauma related to the uterine exploration could well account for the additional morbidity in this group and this should be discussed.

	5. There remain errors in the tables. I haven't checked them all - but 5/57 is not 19% and 10/59 is not 10% and 3/57 is not 3%. These all need checking. I would recommend that the whole database is sent to the editors so that the data can be formally checked against the original entries. The authors state that the tables have all been checked - but this is either not correct or done by someone unable or unwilling to calculate percentages. In all cases it makes the results highly unreliable and i would want to see all the statistics redone by a card-carrying statistician before publication.

REVIEWER	A. Metin Gülmezoglu World Health Organization
REVIEW RETURNED	15-Jun-2017

GENERAL COMMENTS	I am satisfied with the authors' responses.

REVIEWER	Akmal El-Mazny Faculty of Medicine Cairo University Egypt
REVIEW RETURNED	31-May-2017

GENERAL COMMENTS	Thank you for giving me the opportunity to review this interesting study "Uterine balloon tamponade as an adjunct to misoprostol for the treatment of uncontrolled post-partum haemorrhage: a randomized controlled trial in Benin and Mali". Almost all reviewer's comments and recommendations were considered by the authors.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 5 - Akmal El-Mazny

Thank you for giving me the opportunity to review this interesting study "Uterine balloon tamponade as an adjunct to misoprostol for the treatment of uncontrolled post-partum haemorrhage: a randomized controlled trial in Benin and Mali". Almost all reviewer's comments and recommendations were considered by the authors.

Answer (AD): Thank you

Reviewer: 1 - GJ Hofmeyr

This is an important paper because it is to my knowledge the first randomized trial of uterine ballooon tamponade for PPH. Although underpowered for the primary outcome (death or invasive surgery), the trend to increased primary outcome, increased blood transfusion and to increased death (6 versus 1), and the significant increase in blood loss >1000ml alerts global institutions to the urgent need for further randomized trials.

I would suggest 3 minor changes:

1. Background: The authors state that there are no randomized trials of misoprostol for treatment of

PPH - perhaps rather refer to the large WHO study (Widmer et al 2010) which is in the paper's reference list

Answer (AD): Thank you for this suggestion. We now refer to Widmer et al.

Discussion - implications for practice:
2. perhaps add the reference to the WHO Bulletin paper referred to: Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organisation 2009; 87: 666-77 Published online 20 July 2009

Answer (AD): Thank you. We added this reference as you have suggested

3. The statement: "Indeed, the bleedings were controlled by misoprostol in 93% of women in our trial" could perhaps be reworded: "Indeed, the bleeding was controlled in 93% of women in our trial, all of whom received misoprostol. However, as there was no control group who did not receive misoprostol, we cannot be sure in how many cases the bleeding would have ceased without misoprostol".

Answer (AD): Thank you. We reworded the text as you have suggested

Reviewer: 3 A. Metin Gülmezoglu

I am satisfied with the authors' responses.

Answer (AD): thank you !

Reviewer: 2 Andrew Weeks

1. The text remains overenthusiastic about uterine tamponade. Examples of this are seen in the tweetable abstract and the limitations sections following the abstract ("The number of patient included, whose calculation was based on published data, was finally too small to show a significant reduction in the primary outcome"). Similar problems are seen elsewhere.

Answer (AD): We agree with your comment and we changed the tweettable abstract as follows : « Although underpowered, the results of this trial do not support the use of uterine balloon tamponade for the treatment of post-partum haemorrhage » ; and the limitations sections following the abstract, as follows : « Because of a lower than expected incidence of the primary outcome in the control group, the study was underpowered »

2. The blood loss result in the abstract has no RR and 95% CI.

Answer (AD): We added the relative risk 1.52 (95% confidence interval 1.15 to 2.00. p value < 0.01) in the abstract.

3. The response states that "PPH was clinically assessed by the caregivers (midwife or doctor) according to the visual estimation of excessive blood loss and patient status (blood pressure and cardiac frequency)" - this should be added to the methods.

Answer (AD): this sentence was already added in the method section (second paragraph)

4. It is interesting that the methods now suggest that all participants in the balloon tamponade group

had manual uterine exploration whereas that was only done for the 10 women in the misoprostol group who required manual removal of placenta. Trauma related to the uterine exploration could well account for the additional morbidity in this group and this should be discussed.

Answer (AD): We are sorry that our answer to your previous comment about « retained placenta » was unclear. We did not mean that all participants in the balloon tamponade group had manual uterine exploration. In fact, only women with retained placenta had manual exploration. As stated in the Method section, « in both groups, the misoprostol was administered in the rectum (1000 µg) or under the tongue (600 µg) just after randomization and after manual removal of the placenta for women with retained placenta ». The table 2 shows that manual removal of the placenta was not dramatically different between both groups : 6/57 vs 10/59, and we don't think that trauma related to the uterine exploration could account for additional morbidity in the experimental group (tamponade + misoprostol).

5. There remain errors in the tables. I haven't checked them all - but 5/57 is not 19% and 10/59 is not 10% and 3/57 is not 3%. These all need checking. I would recommend that the whole database is sent to the editors so that the data can be formally checked against the original entries. The authors state that the tables have all been checked - but this is either not correct or done by someone unable or unwilling to calculate percentages. In all cases it makes the results highly unreliable and i would want to see all the statistics redone by a card-carrying statistician before publication.

Answer (AD): We are sorry for this mistake. The data manager have copied and pasted the wrong tables (i.e. tables that were not corrected with controled samples). This is the reason why the percentages did not fit with the numerators and the denominators. I checked personally all the tables, and I assume that all percentages are correct. If you wish, the data manager will send you the database when she will be back to the office. She is now on maternity leave until October 2017.

VERSION 3 – REVIEW

REVIEWER	Andrew Weeks University of Liverpool UK
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	I'm happy now. Excellent paper! It will be very well cited and cause enormous discussion amongst the global maternal health community.