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CLINICAL ARTICLE

Obstetrics

Heat stable carbetocin or oxytocin for prevention of postpartum hemorrhage among women at risk: A secondary analysis of the CHAMPION trial

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Abstract

Objective: To examine whether the observed non-inferiority of heat-stable carbetocin (HSC), compared with oxytocin, was influenced by biologic (macrosomia, parity 3 or more, or history of postpartum hemorrhage [PPH]) and/or pharmacologic (induction or augmentation) risk factors for PPH.

Methods: The present study is a secondary analysis of the CHAMPION non-inferiority randomized trial—a two-arm, double-blind, active-controlled study conducted at 23 hospitals in 10 countries, between July 2015 and January 2018. Women with singleton pregnancies, expected to deliver vaginally with cervical dilatation up to 6 cm were eligible. Randomization was stratified by country, with 1:1 assignment. Women in the intervention and control groups received a single intramuscular injection of 100 μg of HSC or 10 IU of oxytocin, respectively. The drugs were administered immediately after birth, and the third stage of labor was managed according to the WHO guidelines. Blood was collected using a plastic drape. For this analysis, we defined a woman as being at risk if she had any one or more of the biologic or pharmacologic risk factor(s).

Results: The HSC and oxytocin arms contained 14 770 and 14 768 women, respectively. The risk ratios (RR) for PPH were 1.29 (95% confidence interval [CI] 1.08–1.53) or 1.73 (95% CI 1.51–1.98) for those with only biologic (macrosomia, parity 3 or more, and PPH in the previous pregnancy) or only pharmacologic (induced or augmented) risk factors, respectively, compared with those with neither risk factors.

Conclusions: Findings reinforce previous evidence that macrosomia, high parity, history of PPH, and induction/augmentation are risk factors for PPH. We did not find a difference in effects between HSC and oxytocin for PPH among women who were neither induced nor augmented or among those who were induced or augmented.

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KEYWORDS
heat-stable carbetocin, management, non-inferiority trial, oxytocin, treatment

1 | INTRODUCTION

Globally, it is estimated that about 300000 women die every year as the result of complications during pregnancy, childbirth, and the postpartum period.[1] In 2017, about 86% of maternal deaths occurred in sub-Saharan Africa and southern Asia combined, where adequate quality of care, infrastructure, timely diagnosis, and treatment are seldom available.[1] Postpartum hemorrhage (PPH) is the leading cause, accounting for almost one-fifth of all maternal deaths globally.[2]

PPH is predominantly due to uterine atony or inadequate contraction of the uterus after childbirth.[2,3] Oxytocin administered immediately after the birth is recommended for PPH prevention worldwide, but it requires cold-chain maintenance.[4,5] Several issues, like availability of functional refrigeration maintained between 2 and 8°C throughout the supply chain and uninterrupted power supply, challenge the efficacy of oxytocin, especially in low- and middle-income countries.[6]

The Carbetocin Hemorrhage Prevention (CHAMPION) trial demonstrated non-inferiority of heat-stable carbetocin (HSC) versus oxytocin for prevention of blood loss of at least 500 mL following delivery or use of additional uterotonic agents.[7] HSC is an alternative uterotonic with a method of action similar to oxytocin, but with no cold-chain requirement. Its active ingredient is stable at room temperature for up to 36 months.[8] Misoprostol is an alternative heat-stable uterotonic for prevention of PPH but has a less acceptable side effect profile compared with HSC and oxytocin. Currently, labeled use of HSC is for PPH prevention only and it is not widely recommended for PPH management.[5]

The CHAMPION trial findings confirm the potential for HSC use in low- and middle-income countries. The trial was conducted in hospitals with well-established resources and infrastructure (e.g., high-quality cold chain, specialists). Approximately 54% of women in the trial underwent induction or augmentation of labor. This bears further examination as oxytocin is frequently used for induction and augmentation. Induction of labor and prolonged first stage of labor (which may lead to augmentation) have been found in meta-analysis to be associated with increased risk of PPH, although previous exposure to oxytocin was not confirmed by meta-analysis despite a suggested association in qualitative analysis.[4,9–11] Therefore, it is important to consider whether the observed non-inferiority of HSC over oxytocin may have been influenced by underlying potential risk factors for PPH—specifically, among women with biologic (macrosomia, parity 3 or more, or previous history of hemorrhage) and/or pharmacologic (induction or augmentation) risk factors.[10,12,13]

The objective of this secondary analysis of the CHAMPION trial data was to assess the differential response to two prophylactic uterotonics (HSC and oxytocin) taking into consideration the presence of biologic or pharmacologic risk factors. We specifically compared the effects of HSC and oxytocin on blood loss (≥500 or ≥1000 mL) among four mutually exclusive subgroups of women: no reported risk factors for PPH (i.e., neither biologic nor pharmacologic risk factors), only biologic risk factors, only pharmacologic risk factors, and both types of risk factors.

2 | MATERIALS AND METHODS

2.1 | Trial design

The CHAMPION trial was a multi-country, two-arm, double-blind, active-controlled, non-inferiority randomized trial that compared HSC with oxytocin for the prevention of PPH during the third stage of labor in women giving birth vaginally, and is described in detail elsewhere.[14] The trial was conducted at 23 hospitals in 10 countries between July 7, 2015 and January 30, 2018. The protocol was approved by each country's ethics committees and regulatory agencies, by the World Health Organization's (WHO) research proposals review panel of the Special Program of Research in Human Reproduction, and by the WHO Ethics Review Committee. All participants provided written informed consent.[7] This secondary analysis used de-identified data and was conducted in close collaboration with the CHAMPION study team.

Women with singleton pregnancies, expected to deliver vaginally, and with cervical dilatation of 6 cm or less were included in the CHAMPION trial.[7] Women were ineligible if they had known allergies to carbetocin, oxytocin homologs, or excipients; or had a serious cardiovascular disorder, serious hepatic or renal disease, or epilepsy. Women were also excluded from the trial if their cervix was dilated more than 6 cm or they were too distressed to provide informed consent. Participation in the trial ended at discharge, transfer to another facility, or death. Information on adverse events including serious events was collected from the time of consent until resolution. Women were included in this secondary analysis if they were part of the CHAMPION modified intention-to-treat (ITT) population of 29 539 participants with information on the use of uterotonics for induction or augmentation. Like the CHAMPION primary analysis, women who withdrew consent, had missing consent or underwent cesarean section were excluded from the modified ITT population.[7]

2.2 | Randomization, intervention, blood loss measurement, and indication of induction or augmentation

Randomization was stratified by country and assigned following a ratio of 1:1.[7] Those assigned to the intervention group received

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a single 100 μg intramuscular injection of HSC and those assigned to the control group received a 10 IU intramuscular injection of oxytocin.

Both drugs were supplied in 1 mL identical ampules in consecutively numbered packs, arranged in dispensers and kept in cold storage. Investigators and participants were blind to treatment assignments.[7]

Immediately after birth, the drug was administered and the third stage of labor was managed according to the WHO guidelines.[15] After the umbilical cord was clamped and cut, a plastic drape was used to collect blood (BRASSS-V Drape) for an hour (or two if bleeding continued), as reported earlier.[7]

The case report form for the CHAMPION trial included whether a participant received any uterotonic for induction or augmentation. However, information on the medication given, route, dose, or timing of these uterotonics were not included. Given this lack of detail, we combined data on augmentation and induction.

2.3 | Statistical analysis

Blood loss of 500 mL or more and 1000 mL or more were the two key outcomes of interest in this secondary analysis. We also report results on use of additional uterotonics, blood transfusion, and additional interventions as described by the CHAMPION trial (e.g., bimanual uterine compression, intrauterine tamponade, uterine cavity exploration under general anesthesia, uterine or hypogastric artery ligation, uterine compression suture, suturing of cervix/high vaginal tear, and hysterectomy).

Biologic risk factors available in the case report forms and used for this analysis included macrosomia, parity 3 or more, or history of PPH. Pharmacologic risk factors included induction or augmentation. Episiotomy or perineal tear, instrumental delivery (vacuum or forceps), and hypertensive disorders were not included because of insufficient evidence of relationship to atony, and the arms were balanced with regards to the proportion of women experiencing these conditions. Multiple gestation is considered a risk factor for PPH, but the CHAMPION trial only included singleton pregnancies, so we could not include multiple gestation in this analysis.[16]

In addition to comparing outcomes for HSC versus oxytocin, we stratified the sample by induced or augmented and neither induced nor augmented to examine any underlying differences in these subgroups. We further stratified the sample into four analytic groups: those with no known risk factors, those with biologic risk factors only, those with pharmacologic risk factors only, and those with both.

For each outcome, a logistic model was used with a binary end point, a binomial distribution, and the log link to obtain risk ratios (RR). The model included terms for trial site and arm (design variables) and a variable for risk factor categorized in the four mutually exclusive groups defined above, including an interaction term for arm by the risk factor. There was no correction for multiple inferences. All hypothesis tests were two-sided and at the 5% significance level. Statistical analysis was conducted using SAS 9.4.

3 | RESULTS

A total of 29 645 participants were recruited for the CHAMPION trial of which 29 539 (99%) participants were in the modified ITT population. One participant had induction/augmentation data missing, leaving 29 538 for this analysis (14 770 [50%] assigned to HSC and 14 768 [50%] assigned to oxytocin). A separate flow diagram is not included here because it is essentially the same as the primary analysis.[7]

Table 1 presents the characteristics of the participants, overall, and the study arms were stratified by induction or augmentation. A little over half 15 999 (54%) of the participants were induced and/or augmented, in both arms. The proportion of participants who were induced or augmented varied considerably across the 10 study sites (Figure S1). Among the induced or augmented group, relatively higher proportions were nulliparous 7566 (47%), in both arms. In comparison, among those who were not induced or augmented, almost half 6709 (49%) had parity 1 or 2, in both arms. Vacuum or forceps delivery was higher 727 (5%) in the induced or augmented group, compared with those who were neither induced nor augmented 420 (3%), in both arms. Episiotomy or tear was also higher in the induced or augmented group 10 485 (65%), in both arms.

Women with only biologic (RR = 1.29, 95% confidence interval [CI] 1.08–1.53) or only pharmacologic risk factors (RR = 1.73, 95% CI 1.51–1.98) were at a higher risk of blood loss of 500 mL or more, compared with those with no risk factor (Table 2). The RR for induction or augmentation was 44% higher than the RR for biologic risk factors (i.e., macrosomia, parity 3 or more, or PPH in the previous pregnancy). Women with both biologic and pharmacologic risk factors had an elevated but statistically non-significant RR for PPH (1.11, 95% CI 0.98–1.25), compared with those with no risk factor (Table 2). Similar analysis for blood loss of 1000 mL or more shows no elevated risk except among those with only pharmacologic risk factors (RR = 2.42, 95% CI 1.72–3.40), compared with those with no risk factor (Table 2). There was no evidence that the risk for PPH among women with both risk factors was more than additive of the two types of risk factors, regardless of the volume of blood loss (≥500 or ≥1000 mL).

Over 10% of women who were induced or augmented had PPH compared with 8% among those who were neither induced nor augmented (Table 3). There is no evidence of difference in RR between the HSC and oxytocin arms for blood loss of 500 mL among those who were neither induced nor augmented (RR = 0.93, 95% CI 0.83–1.05) or among those induced or augmented (RR = 1.02, 95% CI 0.94–1.12). Results for blood loss of 1000 mL or more were similar (Table 3). Additional results for PPH-related outcomes are presented in Table S1 and show no statistically significant difference of risk between HSC and oxytocin, despite induction or augmentation.

Examining 3 common biologic risk factors—macrosomia, parity 3 or more, or PPH in the previous pregnancy—suggests no difference between the HSC and oxytocin arms (Table 4). Although, we found reduced risk of PPH (blood loss ≥500 mL) for HSC (RR = 0.77, 95%

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TABLE 1 Characteristics of study participants, overall and by trial arms, stratified by induction or augmentation during labor.[a]

Characteristic	Total (*N* = 29 538)	Carbetocin (*N* = 14 770)		Oxytocin (*N* = 14 768)	
		Induced or augmented		Induced or augmented	
		No (*n* = 6780)	Yes (*n* = 7990)	No (*n* = 6759)	Yes (*n* = 8009)
Maternal age, year	26.2 ± 5.3	26.2 ± 5.4	26.2 ± 5.2	26.1 ± 5.4	26.3 ± 5.3
Parity					
Nulliparous	12 881 (43.6)	2654 (39.1)	3770 (47.2)	2661 (39.4)	3796 (47.4)
1 or 2	13 380 (45.6)	3332 (49.1)	3333 (41.7)	3338 (49.4)	3377 (42.2)
3 or 4	2759 (9.3)	651 (9.6)	788 (9.9)	605 (9.0)	715 (8.9)
5 or more	518 (1.8)	143 (2.1)	99 (1.2)	155 (2.3)	121 (1.5)
Term or preterm[b]					
Term	26 727 (90.5)	6149 (90.7)	7225 (90.4)	6054 (89.6)	7299 (91.1)
Preterm	2811 (9.5)	631 (9.3)	765 (9.6)	705 (10.4)	710 (8.9)
Instrumental delivery (vacuum or forceps)	1147 (3.9)	206 (3.0)	361 (4.5)	214 (3.2)	366 (4.6)
Episiotomy or perineal tear	18 450 (62.5)	3979 (58.7)	5228 (65.4)	3986 (59.0)	5257 (65.6)
Hypertensive disorders of pregnancy	646 (2.2)	84 (1.2)	243 (3.0)	79 (1.2)	240 (3.0)
Birth weight, g	3075 ± 528	3069 ± 512	3078 ± 536	3059 ± 523	3090 ± 536
Birth weight, g					
Below 2500	2965 (10.0)	704 (10.4)	788 (9.9)	729 (10.8)	744 (9.3)
2500–3999	25 467 (86.2)	5864 (86.5)	6881 (86.1)	5796 (85.8)	6926 (86.5)
4000 or more	1106 (3.7)	212 (3.1)	321 (4.0)	234 (3.5)	339 (4.2)
Parous women	16 657 (56.4)	4126 (60.9)	4220 (52.8)	4098 (60.6)	4213 (52.6)
Previous CS among parous women	892 (5.4)	289 (7.0)	144 (3.4)	314 (7.7)	145 (3.4)
Previous PPH among parous women	249 (1.5)	53 (1.3)	68 (1.6)	57 (1.4)	71 (1.7)

Abbreviations: CS, cesarean section; PPH, postpartum hemorrhage.

[a]Data are presented as mean ± standard deviation or as number (percentage).

[b]Term, 37 completed weeks or more of pregnancy; Preterm, less than 37 completed weeks of pregnancy.

TABLE 2 The risk of blood loss (≥500 and ≥1000 mL) in four mutually exclusive subgroups.

Outcome	Risk factor	*n*/*N* (%)[c]	RR (95% CI)	*P* value
Blood loss ≥500 mL	No risk factor	842/11559 (7.3)	1.00	
	Biologic risk factors only[a]	207/1947 (10.6)	1.29 (1.08–1.53)	0.004
	Induced and/or augmented only	1366/13654 (10.0)	1.73 (1.51–1.98)	<0.001
	Both risk factors[b]	255/2309 (11.0)	1.11 (0.98–1.25)	0.103
Blood loss ≥1000 mL	No risk factor	104/11559 (0.9)	1.00	
	Biologic risk factors only[a]	47/1947 (2.4)	1.15 (0.77–1.71)	0.501
	Induced and/or augmented only	229/13654 (1.7)	2.42 (1.72–3.40)	<0.001
	Both risk factors[b]	57/2309 (2.5)	1.19 (0.89–1.60)	0.236

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Biologic risk factors include macrosomia, parity 3 or more, and postpartum hemorrhage in the previous pregnancy.

[b]Women who had biologic risk factors and were induced/augmented.

[c]The denominator in this table is 29 469 because 69 cases had missing blood loss information.

CI 0.62–0.95), compared with oxytocin in macrosomic pregnancies. However, these findings were not consistent across outcomes, with an inconsistent result for blood loss of 1000 mL or more (RR = 1.32, 95% CI 0.82–2.13) (Table 4). Additional results, shown in Table S2, for PPH-related outcomes show no statistically significant difference of risk for PPH between treatment arms.

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TABLE 3 The effect[a] of carbetocin and oxytocin on blood loss (≥500 or ≥1000 mL) among women who were induced or augmented during labor.

Outcome	Induced or augmented	Carbetocin *n/N* (%)	Oxytocin *n/N* (%)	RR (95% CI)	*P* value for arm comparison[b]	*P* value for difference in RR[c]
Blood loss ≥500 mL	No	509/6763 (7.5)	540/6743 (8.0)	0.93 (0.83–1.05)	0.248	0.222
	Yes	818/7973 (10.3)	803/7990 (10.1)	1.02 (0.94–1.12)	0.617	
Blood loss ≥1000 mL	No	72/6763 (1.1)	79/6743 (1.2)	0.91 (0.66–1.25)	0.556	0.288
	Yes	151/7973 (1.9)	135/7990 (1.7)	1.12 (0.89–1.41)	0.317	

Abbreviations: CI, confidence interval; RR, relative risk.

[a]The effect estimates are relative risks and the models' included terms for intervention or control, study site, induction or augmentation of labor and a product term for interaction between arm and induction or augmentation of labor.

[b]The *P* value compares the two arms (carbetocin versus oxytocin) within each stratum of induced or augmented (yes or no). In other words, compares two columns within each row of the table.

[c]This *P* value compares the RR in the two strata of induced or augmented (yes or no).

TABLE 4 The effect[a] of carbetocin and oxytocin on blood loss and related complications among those with biologic risk factors at the time of labor for postpartum hemorrhage.

Outcome	Risk factors	Stratum	Carbetocin *n/N* (%)	Oxytocin *n/N* (%)	RR (95% CI)	*P* value for difference in RR
Blood loss ≥500 mL[b]	Macrosomia	No	1234/14210 (8.7)	1203/14160 (8.5)	1.02 (0.95, 1.10)	0.015
		Yes	93/527 (17.6)	140/573 (24.4)	0.77 (0.62–0.95)	
	Parity 3 or more	No	1203/13059 (9.2)	1240/13138 (9.4)	0.98 (0.91–1.05)	0.309
		Yes	124/1678 (7.4)	103/1595 (6.5)	1.12 (0.87–1.42)	
	PPH in previous pregnancies	No	1292/14616 (8.8)	1303/14606 (8.9)	0.99 (0.92–1.06)	0.848
		Yes	35/121 (28.9)	40/127 (31.5)	0.95 (0.67–1.37)	
Blood loss ≥1000 mL[b]	Macrosomia	No	191/14210 (1.3)	185/14160 (1.3)	1.02 (0.84–1.25)	0.332
		Yes	32/527 (6.1)	29/573 (5.1)	1.32 (0.82–2.13)	
	Parity 3 or more	No	198/13059 (1.5)	198/13138 (1.5)	1.01 (0.83–1.23)	0.281
		Yes	25/1678 (1.5)	16/1595 (1.0)	1.44 (0.78–2.68)	
	PPH in previous pregnancies	No	211/14616 (1.4)	204/14606 (1.4)	1.03 (0.85–1.25)	0.637
		Yes	12/121 (9.9)	10/127 (7.9)	1.26 (0.57–2.81)	

Abbreviations: CI, confidence interval; PPH, postpartum hemorrhage; RR, relative risk.

[a]The estimates are relative risks and the models' included terms for intervention or control and the study sites.

[b]Denominator for these results is 29 470 because the single individual missing for induction/augmentation was included in this analysis.

Serious adverse events such as maternal death or severe complications including admission to intensive care unit, hysterectomy, blood loss of more than 2 L, or uterine inversion were observed in 26 (0.2%) and 23 (0.2%) cases in the HSC and oxytocin groups, respectively. This information was missing for 69 participants. Newborn deaths were observed in 49 (0.3%) and 47 (0.3%) cases, in the HSC and oxytocin groups, respectively. More details on these events have been reported previously.[7]

4 | DISCUSSION

This secondary analysis of the CHAMPION trial data reaffirms prevailing knowledge that macrosomia, parity of 3 or more, and history of PPH are risk factors for PPH in the index pregnancy. Further, we are reminded that PPH also occurs in cases with no risk factors as 7% of women with no identified risk factors bled 500 mL or more and 1% bled 1000 mL or more. Results show that the magnitude of the risk for PPH from biologic risk factors is less than it is for induction and/or augmentation. This is notable given that more than half of the women in the study received some form of induction or augmentation, and about 15% had blood loss of 500 mL or more or needed additional uterotonic treatment. Most of these cases were likely exposed to oxytocin, potentially decreasing the effectiveness of either oxytocin or HSC used for preventive purposes as a result of already occupied oxytocin receptors. Some cases may have received misoprostol for induction, though we cannot distinguish them from those that received oxytocin for induction.[17,18] Although induction and/or augmentation is an important tool to improve outcomes when indicated, over-use is a modifiable medically imposed

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risk factor. Indeed, several countries in the trial documented induction rates as high as 48% and augmentation rates as high as 92% (Table S2).

Our finding adds to the conflicting body of literature on induction-associated increased risk for PPH. Some studies demonstrate induction with either oxytocin or prostaglandins is associated with higher risk for PPH among low-risk women, but other studies show no association.[9,19,20] Although these previous studies were conducted in high-income settings, the practices of augmentation and induction are becoming more commonplace, globally. Our finding calls attention to the importance of monitoring both rates and indications for augmentation and induction to avoid iatrogenic PPH caused by unindicated practices.

The findings reaffirm the non-inferiority demonstrated for HSC compared with oxytocin, even in the context of pharmacologic and biologic risk factors. To our surprise, we found that women who had one or more biologic risk factors and were also induced and/or augmented did not have increased risk for PPH. Although difficult to explain, one speculation could be that women identified as having both risk factors may have received closer monitoring, with more aggressive intervention at blood losses less than 500 mL. Because of the presence of both types of risk factors some of these high-risk cases may have undergone cesarean sections, which were excluded from the modified ITT analysis.

Given the longer half-life of HSC and the stronger clinical response, one might expect HSC to have shown superiority to oxytocin for prevention of PPH in the presence of risk factors, particularly induction and/or augmentation. In case of PPH following either the use of oxytocin or HSC for prevention, the first line of treatment for PPH management is currently oxytocin. If all the binding receptors are already occupied, further treatment is unlikely to be effective for atony. Results from this secondary analysis suggest that this may not be the case, given non-significant differences in PPH across both arms. However, the lack of granular data on induction and/or augmentation medication choice, dosing protocol, and duration of exposure may have influenced the outcome.

The results should be interpreted in the context of several strengths and weaknesses. The robust design strengthens the internal validity of the results. Another strength is the objective measurement of blood loss, minimizing measurement error. The generalizability of this evidence may be limited, especially to populations in lower-level facilities, in low-resource settings. This secondary analysis has limited power because the trial was powered to measure non-inferiority of HSC and it did not have the sample size to detect a differential effect of the drug by induction and/or augmentation status. Another limitation of this analysis is the lack of information on timing, duration, or dosage used for induction or augmentation, with a wide range of predelivery exposures to oxytocin likely. We also do not know in which cases misoprostol was used. Further, the increased risk of PPH associated with induction and/or augmentation might be partially accounted for by blood loss from episiotomy or tears. However, this is unlikely to have influenced our primary conclusions because episiotomy and tears were balanced across arms. Lastly, previous literature suggests that multiple pregnancy may be a risk factor for blood loss, which we could not include in our biologic risk factor group as multiple pregnancies were excluded.

In conclusion, this secondary analysis suggests that induction and/or augmentation is associated with PPH, in addition to known biologic risk factors. However, while the latter cannot be modified, the former represents a practice that warrants careful adherence to medical guidelines.

AUTHOR CONTRIBUTIONS

Dilys Walker conceptualized the study, interpreted the results, and revised the manuscript critically. Olorunfemi Owa contributed to the conceptualization and critical revision of the manuscript. Rakesh Ghosh guided the analysis, drafted the manuscript, and organized the tables and figures. Nicole Santos and Elizabeth Butrick contributed to conceptualization, interpretation of results, and critical revision of the manuscript. Gilda Piaggio conducted the analysis, contributed to interpretation, and drafted sections of the manuscript. Mariana Widmer and Fernando Althabe informed the conceptualization, linked the study team to the trial group, and provided critical revision of the manuscript. Zahaida Qureshi, Pisake Lumbiganon, and Geetanjali Katageri contributed to interpretation of results and critical revision of the manuscript. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

TRIAL REGISTRATIONS

Australian New Zealand Clinical Trials Registry number: ACTRN12614000870651 https://www.anzctr.org.au/TrialSearch.aspx#&&conditionCode=&dateOfRegistrationFrom=&interventionDescription=&interventionCodeOperator=OR&primarySponsorType=&gender=&distance=&postcode=&pageSize=20&ageGroup=&recruitmentCountryOperator=OR&recruitmentRegion=&ethicsReview=&countryOfRecruitment=&registry=&searchTxt=ACTRN12614000870651&studyType=&allocationToIntervention=&dateOfRegistrationTo=&recruitmentStatus=&interventionCode=&healthCondition=&healthyVolunteers=&page=1&condi

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EU Clinical Trials Register: 2014–004445-2https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-004445-266

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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