क्षेत्रीय आयुर्विज्ञान संस्थान, इंफाल: मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
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CIRCULAR

Imphal, the 17th July, 2025

No. 132/RIMS-MRU/2025: The **3rd Research Masterclasses 2025**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, **on 25th July, 2025 (Friday).**

2. All the faculties (RIMS, Dental College, College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) are invited to take part in the session at Banting Hall, RIMS, Imphal.

Date: 25.07.2025 (Friday)
Time: 3:00 PM onwards
Venue: Banting Hall, RIMS, Imphal

3. As per the directives issued by the DHR, **maximum participation** from our institute is strongly encouraged. MRU is submitting the attendance sheet to the DHR after the session concludes.

4. The research papers to be discussed during the research masterclass are available in the RIMS website: https://www.rims.edu.in/secure/ and also being shared with all concerned through their respective e-mail IDs.

17/07/2025

Prof. T. Jeetenkumar Singh,
Nodal Officer,
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH for kind information
3. The Dean (Academic), RIMS for kind information & permission to utilize the facilities at Banting Hall.
4. The Principal, Dental College, RIMS
5. The Principal, College of Nursing, RIMS
6. The Head of Department, RIMS, Imphal

   (4–6: with a request for ensuring maximum participation.)
7. The Chairperson/Co-Chairperson/Member, LRAC, MRU, RIMS.....
8. The Member, EC, MRU, RIMS, Imphal.....
9. The Principal Investigator, RIMS .....
10. The IT section, RIMS – with a request for uploading the notice in the website & technical support on 25.7.25
11. Asst. Engineer (Elect./Civil), RIMS - with a request for ensuring uninterrupted power supply & optimum AC functioning.
12. The Care Taker, Banting Hall, RIMS, Imphal- for proper upkeep of the venue & the accompanying facilities.
13. Guard file.

No. R.11016/22/2024-HR
Government of India
Ministry of Health & Family Welfare
Deptt of Health Research

IRCS Building, 2nd Floor,
Red Cross Road
New Delhi – 110 001
15.07.2025

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses, 2025 for MRU network– reg.

Sir/Madam

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' on last Friday of each month from 3:00-4:30 PM. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The next Research Masterclass is scheduled for **25.07.2025 (Friday) at 3:00 PM**. The invited speaker is **Prof. Shivaprasad Goudar**, Professor of Physiology, Women's and Children's Health Research Unit, Jawahar Lal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Also, it is requested from your institute to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 23.07.2025. These questions will be discussed with the speaker during masterclass.

Yours faithfully

(Dharkat R. Luikang)
Deputy Secretary

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

Widmer et al. Trials (2016) 17:143
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Trials

Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally: study protocol for a randomized controlled trial

Mariana Widmer[1*], Gilda Piaggio[2], Hany Abdel-Aleem[3], Guillermo Carroli[4], Yap-Seng Chong[5], Arri Coomarasamy[6], Bukola Fawole[7], Shivaprasad Goudar[8], G. Justus Hofmeyr[9], Pisake Lumbiganon[10], Kidza Mugerwa[11], Thi My Huong Nguyen[1], Zahida Qureshi[12], Joao Paulo Souza[13] and A. Metin Gülmezoglu[1]

Abstract

Background: Postpartum haemorrhage (PPH) is the leading cause of maternal mortality in low-income countries and contributes to nearly a quarter of maternal deaths globally. The current available interventions for prevention of postpartum haemorrhage, oxytocin and carbetocin, are limited by their need for refrigeration to maintain potency, as the ability to maintain a cold chain across the drug distribution and storage network is inconsistent, thus restricting their use in countries with the highest burden of maternal mortality. We describe a randomized, double-blind non-inferiority trial comparing a newly developed room temperature stable formulation of carbetocin to the standard intervention (oxytocin) for the prevention of PPH after vaginal birth.

Methods/design: Approximately 30,000 women delivering vaginally will be recruited across 22 centres in 10 countries. The primary objectives are to evaluate the non-inferiority of room temperature stable carbetocin (100 μg intramuscular) versus oxytocin (10 IU intramuscular) in the prevention of PPH and severe PPH after vaginal birth. The primary endpoints are blood loss ≥500 mL or the use of additional uterotonics (composite endpoint required by drug regulatory authorities) and blood loss ≥1,000 mL (WHO requirement). Non-inferiority will be assessed using a two-sided 95 % confidence interval for the relative risk of the above endpoints for room temperature stable carbetocin versus oxytocin. The upper limit of the two-sided 95 % confidence interval for the relative risk for the composite endpoint of blood loss ≥500 mL or the use of additional uterotonics, and for the endpoint of blood loss ≥1,000 mL, will be compared to a non-inferiority margin of 1.16 and 1.23, respectively. If the upper limit is below the corresponding margin, non-inferiority will have been demonstrated. The safety analysis will include all women receiving treatment. Safety and tolerability will be assessed by a review of adverse events, by conducting inferential testing with significance levels for between-group comparisons.

(Continued on next page)

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(Continued from previous page)

Discussion: If the results of the study show that room temperature stable carbetocin is a safe and effective alternative to oxytocin, this could have a substantial impact on the prevention of postpartum haemorrhage and maternal survival worldwide.

Trial registration: ACTRN12614000870651 (14 August 2014)

Keywords: Postpartum haemorrhage, Room temperature stable carbetocin, Oxytocin, Non-inferiority trial

Background

Postpartum haemorrhage (PPH) is defined as a blood loss of ≥500 mL within 24 hours of delivery, while severe PPH (sPPH) is defined as a blood loss of ≥1,000 mL within the same time frame [1]. PPH is the leading cause of maternal mortality in low-income countries, contributing to nearly a quarter of maternal deaths globally. In addition, PPH is a significant contributor to severe maternal morbidity and long-term disability, as well as to a number of other severe maternal conditions generally associated with more substantial blood loss, including shock and organ dysfunction [2–4]. Improving health care for women during childbirth in order to prevent and treat PPH is an essential step towards the achievement of the United Nations Millennium Development Goals.

The majority of deaths due to PPH could be avoided through the use of prophylactic uterotonics during the third stage of labour and by timely and appropriate management. Injectable oxytocin has been recommended by the World Health Organization (WHO) for routine use during the third stage of labour and is the preferred drug for the prevention and management of blood loss after childbirth; however, several studies have demonstrated that oxytocin loses potency in field conditions, particularly in tropical climates [1, 5, 6]. To decrease potency loss due to degradation, oxytocin must be either stored at controlled room temperature (25 °C or lower) for a restricted amount of time or refrigerated (2 °C to 8 °C), making its use difficult in low resource settings. To ease this barrier, several groups have been researching heat stable oxytocin formulations [5]. Though some progress has been made in this area, there is currently no heat stable oxytocin formulation for therapeutic use [7].

Carbetocin (1-deamino-1-monocarba-(2-O-methyl-tyrosine)-oxytocin) is a long-acting synthetic agonist analogue of the human oxytocin, and it appears to be a promising agent in the prevention of PPH following vaginal delivery. The clinical and pharmacological properties of carbetocin are similar to those of oxytocin. However, carbetocin is a more stable molecule and induces a prolonged uterine response, when administered postpartum, in terms of both amplitude and frequency of contractions due to its longer half-life [8–10]. In a Cochrane systematic review including 11 studies (2,635 women), the use of carbetocin resulted in a statistically significant reduction in the use of additional/therapeutic uterotonics compared to oxytocin for those who underwent caesarean delivery (risk ratio (RR) 0.62; 95 % confidence interval (CI) 0.44 to 0.88; four trials, 1,173 women), but not for vaginal delivery. Compared to oxytocin, carbetocin was associated with reduced uterine massage following both caesarean delivery (RR 0.54; 95 % CI 0.37 to 0.79; two trials, 739 women) and vaginal delivery (RR 0.70; 95 % CI 0.51 to 0.94; one trial, 160 women). There were no statistically significant differences between carbetocin and oxytocin in terms of risk of any PPH or in risk of sPPH [11].

Carbetocin is currently approved in multiple countries for the prevention of PPH during caesarean section. The drug is licensed to be administered by slow intravenous (IV) single injection at a dose of 100 μg. Its current formulation requires refrigeration.

A room temperature stable (RTS) variant of carbetocin has recently been developed and is now approved in the European Union; this variant differs from the current carbetocin formulation only in its excipients (Table 1). The stability data from long-term studies performed at 30 °C and 75 % relative humidity, as well as accelerated at 40 °C and 75 % relative humidity, indicate a shelf life of at least 36 months at 30 °C for the new RTS formulation of carbetocin. Carbetocin RTS therefore represents a promising intervention for reducing PPH, particularly in settings where cold storage is difficult to achieve and maintain. Here, we describe a planned randomized trial to evaluate the non-inferiority of carbetocin RTS versus oxytocin after vaginal delivery in the prevention of PPH and sPPH.

Methods/design

Primary objectives and hypotheses

The trial has two primary objectives: 1) To evaluate non-inferiority of carbetocin RTS versus oxytocin after vaginal delivery in the prevention of the composite endpoint "blood loss of 500 mL or more or the use of additional uterotonics" at one hour and up to two hours for women who continue to bleed after one hour; and 2) to evaluate non-inferiority of carbetocin RTS versus oxytocin in the prevention of sPPH (≥1,000 mL blood loss) at one hour and up to two hours for women who continue to bleed after one hour.

Table 1 Composition of carbetocin RTS and carbetocin

New carbetocin RTS formulation			Current carbetocin refrigerated formulation (Duratocin®, Ferring)[a]		
Component	Amount (mg/mL)	Function	Component	Amount (mg/mL	Function
Carbetocin	0.100	Active substance	Carbetocin	0.100	Active substance
Succinic acid	1.19	Buffer	Sodium chloride	9	Isotonicity agent
Mannitol	47.0	Isotonicity agent	Glacial acetic acid	to pH 3.8	pH adjustment
L-methionine	1.00	Antioxidant	Water for injection	1.0 mL	Solvent
Sodium hydroxide 2 N	to pH 5.45	pH adjustment	–	–	–
Water for injection	1.0 mL	Solvent	–	–	–

[a]Carbetocin 100 μg/mL was first approved in Canada in June 1997 and is currently registered in more than 70 countries under the trade names PABAL/DURATOCIN/LONACTENE/DURATOBAL
RTS room temperature stable

For both objectives the hypotheses are: 1) carbetocin RTS is non-inferior to oxytocin in terms of the proportion of women with blood loss ≥500 mL or the use of additional uterotonic drugs after vaginal delivery within a non-inferiority margin of 1.16 on the relative risk scale, and the proportion of women with blood loss ≥1,000 mL after vaginal delivery within a non-inferiority margin of 1.23 on the relative risk scale; and 2) carbetocin RTS is superior to oxytocin in terms of the proportion of women with blood loss ≥500 mL or use of additional uterotonic drugs, and in terms of the proportion of women with blood loss ≥1,000 mL after vaginal delivery. For each of the two primary endpoints, superiority will be tested if non-inferiority has been demonstrated.

Investigators and other assessors will be blinded to individual treatment allocation. The study will be conducted by the HRP/WHO, and WHO staff will also remain blinded to individual participant treatment allocation during the conduct of the trial.

Study drug

Carbetocin RTS (Ferring, St. Prex, Switzerland) will be administered as a single IM dose of 100 μg in a 1 mL solution. Oxytocin 10 IU/mL (Syntocinon®, Novartis, Basel, Switzerland) will be administered as a single intramuscular (IM) dose in a 1 mL solution. In order to maintain the blindness of the trial, carbetocin RTS and oxytocin will be provided in 1 mL ampoules in consecutively numbered treatment packs arranged in dispensers and will be stored in a refrigerator at 2 °C to 8 °C.

Study design

This clinical trial will be conducted in compliance with the clinical trial protocol, good clinical practice and the applicable regulatory requirements. The trial is planned to be conducted at 22 centres in 10 countries: Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda and the United Kingdom. Approximately 30,000 women will be included in the trial. The recruitment period will be approximately 12 months in each country.

The care provider in charge of antenatal care visits at the hospital will inform potentially eligible pregnant women (women with no allergies to carbetocin, other oxytocin homologues or excipients, or serious cardiovascular disorders) about the trial.

At admission for labour at the hospital, the woman will be approached for participation in the trial when she is in early labour and if her vital signs are normal, and she is not stressed. The investigator will invite her to sign the informed consent. Informed consent will be obtained before any trial-related procedures are carried out.

During the second stage of labour when vaginal delivery is imminent, the woman will be randomized to receive either a single dose of oxytocin 10 IU IM or a single dose of carbetocin RTS 100 μg IM.

The investigator will administer the investigational medicinal product (IMP) immediately after the birth of the baby (preferably within one minute). Once the IMP has been administered, the investigator will follow the management of the third stage of labour as recommended in WHO guidelines and as detailed in the trial's manual of operations.

Once the cord is clamped (1–3 minutes after delivery of the baby) and cut, the investigator will place a calibrated drape under the woman's buttocks and blood loss will be measured for one hour or two hours postpartum if the bleeding continues beyond one hour (blood loss measuring details are provided in the trial's manual of operations).

The woman will end her participation in the trial after her discharge or if she is transferred to a higher care unit, such as an intensive care unit (ICU). Data will be entered into a validated online database system compliant with the FDA 21 CFR part 11.

The trial master protocol was approved by the World Health Organization Research Ethics Review Committee. All sites received ethics approval from their institutional/national boards (see additional file 1 for the list of ethics committees that reviewed and approved the proposal).

Inclusion/exclusion criteria

Women will be eligible for inclusion into this trial if they are expected to deliver vaginally, have a cervical dilatation equal to or less than 6 cm, have a known singleton pregnancy and have provide written informed consent. Women will not be eligible for study participation if they: 1) are in an advanced first stage of labour (>6 cm cervical dilatation) or are too distressed to understand, confirm and give informed consent regardless of cervical dilatation; 2) are non-emancipated minors (as per local regulations) without a guardian; 3) have been scheduled for a planned caesarean section; 4) have a birth considered to be an abortion according to local guidelines; 5) have known allergies to carbetocin, other oxytocin homologues or excipients in the medicinal products used in the trial; 6) have serious cardiovascular disorders; 7) have serious hepatic or renal disease; 8) have epilepsy; or 9) are not capable of giving consent due to other health problems such as obstetric emergencies (for example, antepartum haemorrhage) or mental disorder.

Participants will be free to discontinue the trial at any time without giving their reason(s). Participants who withdraw will not be replaced; that is, randomized numbers will be uniquely linked to each participant. Data collected up to that point will be included unless participants request the opposite. After a participant has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial centre's standard of care and generally accepted medical practice and depending on the participant's individual medical needs.

Randomization

The random allocation sequence will be generated centrally at WHO headquarters using computer-generated random numbers. Randomization will be stratified by country and will use permuted blocks, with an allocation ratio of 1:1. Participants will randomly be assigned within each country to one of the two treatment groups: oxytocin 10 IU IM or carbetocin RTS 100 μg IM. Allocation of the randomly generated sequence will be performed by consecutively numbered treatment packs arranged in dispensers.

Primary and secondary endpoints

The primary and secondary endpoints are listed in Table 2. The trial is being conducted as an effectiveness trial with the objective of carbetocin RTS being registered for the indication "prevention of postpartum haemorrhage" by drug regulatory authorities if it is shown to be non-inferior or superior to oxytocin. The primary composite endpoint is blood loss ≥500 mL or use of additional uterotonics. For the purpose of evaluating clinical effectiveness and for the potential inclusion of carbetocin RTS in future WHO guidelines and the Model List of Essential Medicines, the more substantive endpoint of blood loss ≥1,000 mL is also a primary endpoint. Since the two primary endpoints serve independent objectives, there will be no adjustment for the type I error rate for multiplicity of endpoints.

Table 2 Primary and secondary endpoints

Primary endpoints
The proportion of women: • with blood loss of 500 mL or more or the use of additional uterotonics at one hour and up to two hours for women who continue to bleed after one hour; • with blood loss of 1,000 mL or more at one hour and up to two hours for women who continue to bleed after one hour.
Secondary endpoints
The proportion of women: • with blood loss of 500 mL or more at one hour (or two hours postpartum if the bleeding continues beyond one hour); • receiving additional uterotonics at one hour (or two hours postpartum if the bleeding continues beyond one hour); • receiving additional uterotonics up to time of discharge; • receiving blood transfusion up to time of discharge; • with manual removal of placenta up to time of discharge; • having additional surgical procedures (for example, suturing of cervix/high vaginal tear, exploration of uterine cavity under general anaesthetic, uterine compression suture, uterine or hypogastric ligation, hysterectomy) up to time of discharge; • with maternal death; • with composite outcome of maternal death or severe morbidity (admission to intensive care unit, hysterectomy, blood loss of two litres or more, uterine inversion) up to time of dischargeBlood loss in mL at one hour (or two hours postpartum if the bleeding continues beyond one hour). The incidence and severity of adverse or serious adverse events up to the time of discharge. Newborn outcomes (vital status, Apgar score at 5 minutes, resuscitation of the baby, mechanical ventilation).

Assessment of efficacy

Efficacy will be assessed using blood loss volume measurement per the two primary endpoints listed in Table 2. Blood loss will be measured using a calibrated drape [12], which will be placed under the participant's buttocks once the cord is clamped (1–3 minutes after delivery of the baby) and cut. Blood loss will be measured for one hour, or for two hours postpartum, if the bleeding continues beyond one hour. Blood loss weight in grams will be converted to millilitres by dividing the figure in grams by 1.06 (blood density in grams per millilitre) [13].

Assessment of safety

Comprehensive assessment of the safety of the study drugs will be performed throughout the course of the trial, from the time of the participant's signature of informed consent until discharge. Trial centre personnel will report any adverse event (AE), whether observed by the investigator or reported by the participant.

The intensity of an AE will be classified using a three-point scale: mild — awareness of signs or symptoms, but no disruption of usual activity; moderate — event sufficient to affect usual activity; and severe — inability to work or perform usual activities. AEs will also be classified as possibly related to study drug (that is, there is evidence or argument to suggest a causal relationship between the AE and the study drug), or not related to study drug (that is, there is no reasonable evidence or argument to suggest a causal relationship between the AE and the study drug).

The outcome of an AE will be classified as: recovered/resolved (fully recovered or the condition has returned to the level observed at initiation of trial treatment); recovered/resolved with sequelae (resulted in persistent or significant disability/incapacity); recovering/resolving; not recovered/not resolved; or fatal.

An AE will be considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. If an investigator becomes aware of a serious AE after the participant's hospital discharge, and he/she assesses the serious AE to have a reasonable possible causality to the study drug, the case will be reported, regardless of how long after the end of the trial the AE took place.

Since the amount of blood lost is collected as an efficacy endpoint, only the following blood loss events that fulfil the criteria for a serious AE will be recorded: ICU admission (adult ICU admission, not maternity/labour ward high care); surgical intervention for control of haemorrhage (hypogastric artery ligation or uterine compression sutures); peripartum hysterectomy, blood loss ≥ 2,000 mL; and uterine inversion.

Sample size calculation

The two endpoints that guided the sample size estimation for the trial were sPPH (blood loss ≥1,000 mL), PPH (blood loss ≥500 mL) or the use of additional uterotonics. Severe PPH is a more serious endpoint that is closely associated to severe maternal morbidity and related to additional interventions. The sPPH endpoint is also less frequent and thus guided the overall sample size estimation.

A non-inferiority design was chosen since the aim of the trial is to determine if carbetocin RTS is non-inferior in efficacy to the standard intervention (oxytocin 10 IU IM). In order to demonstrate non-inferiority within a margin of 0.46 %, with a power of 80 % and with a significance level of 2.5 %, a total of 29,082 women are needed assuming an equal sPPH prevalence of 2 % with both treatments, calculated by the standard formula (see Additional file 2 for the rationale of the choice of the margin) [14]. The margin of 0.46 % on the difference scale corresponds to 1.23 on the relative scale for the assumed prevalence. Figure 1 shows the total sample size required to assess non-inferiority at the 2.5 % level of significance (usually required for non-inferiority trials) for different scenarios. We also assumed, from a similar large trial [15], a 3 % loss of study participants who are eligible to contribute to the analysis due to exclusion of women

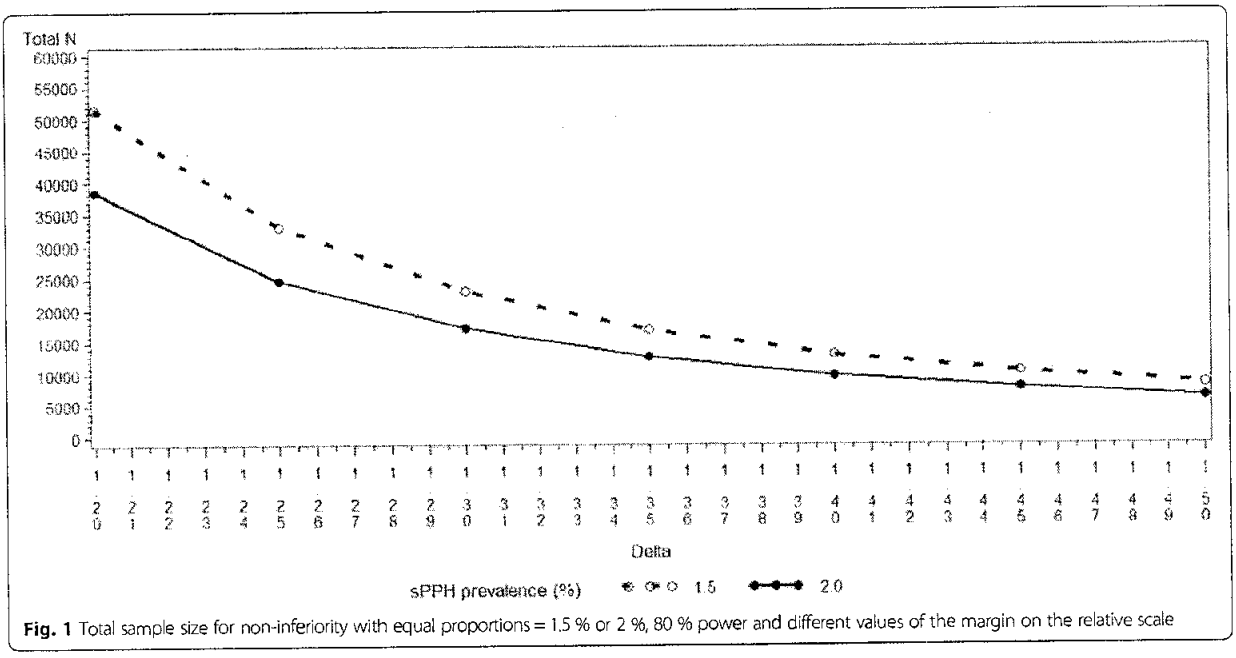

Fig. 1 Total sample size for non-inferiority with equal proportions = 1.5 % or 2 %, 80 % power and different values of the margin on the relative scale

with a caesarean section or abortion after randomization, and those who are not protocol-compliant (excluded only in the per-protocol analysis), bringing the sample size to 30,000. This sample size will provide 90 % power for a conventional two-sided 5 % test of superiority to detect a minimum significant difference between 1.5 % and 2 % in the rate of sPPH for the two treatment groups.

Similarly, we calculated the sample size for the composite endpoint defined as blood loss ≥500 mL or administration of additional uterotonics. With active management, the risk of this event is estimated as 16 % (personal communication) [15]. Assuming equal prevalence for this event of 16 % with both treatments, in order to demonstrate non-inferiority within a margin of 1.16 on the relative scale, with a power of 80 % and with a significance level of 2.5 %, a total of 6,242 women are needed. With 30,000 women the power obtained would be more than 99 % [14]. This sample size will provide a power of 99.5 % for a conventional two-sided 5 % test of superiority to detect a minimum significant difference between 16 % and 18 % in the occurrence of PPH or administration of additional uterotonics for the two treatment groups (Stata version 13.1).

Analysis populations

Analyses will be performed in three populations: intention-to-treat (ITT), modified ITT, and per-protocol. The ITT population includes all randomized participants, using the treatment as randomized. The modified ITT analysis excludes women having a caesarean section after randomization and those withdrawing consent. The per-protocol population includes all participants randomized into the trial, who were compliant with, and treated according to, the protocol, and who fulfil the following criteria: compliance with all entry criteria, absence of major clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment, and adequate compliance with trial medication (giving oxytocin or carbetocin to women as randomized). Declaring carbetocin RTS non-inferior to oxytocin will require non-inferiority to be demonstrated for both per-protocol and the modified ITT analyses. For testing the superiority of each endpoint, the modified ITT analysis will be the main analysis. The primary population for safety analysis will consist of all women receiving treatment.

Statistics

Safety and tolerability will be assessed by a review of AEs, by conducting inferential testing with significance levels for between-group comparisons. The between-treatment difference for the occurrence of AEs will be tested using the stratified Mantel-Haenszel chi-square if frequencies are sufficiently high, or otherwise with exact methods taking stratification into account.

For efficacy, non-inferiority will be assessed using a two-sided 95 % confidence interval (CI) for the relative risk (RR) of sPPH and of PPH or additional uterotonic use (carbetocin RTS versus oxytocin). The upper limit of the two-sided 95 % CI for the RR for the composite endpoint of blood loss ≥500 mL or additional uterotonic use will be compared to the non-inferiority margin of 1.16. The upper limit of the two-sided 95 % CI for the RR for the endpoint of blood loss ≥1,000 mL will be compared to the non-inferiority margin of 1.23. If the upper limit is below the corresponding margin, non-inferiority will have been demonstrated. This upper limit is the same as the upper limit of the one-sided 97.5 % CI; therefore, the significance level for the non-inferiority test will be 2.5 % (one-sided). For each endpoint, to declare carbetocin RTS non-inferior to oxytocin, we will require non-inferiority to be demonstrated for both PP and the modified ITT analyses. If non-inferiority is demonstrated, a two-tailed superiority test will be conducted at 5 % level of significance. Interpretation will be as in Fig. 1 of Piaggio et al. [16]. Comparisons will also be expressed as risk differences with 95 % CIs.

The statistical technique used to conduct tests and obtain CIs for the main endpoints will be a logistic model with a binary endpoint, a binomial distribution and the log link to obtain RRs. The identity link will be used to obtain risk differences. Stratifying variables (country) will be included in the model. The model will be fitted using SAS Software version 9.3 (SAS Institute Inc., Cary, NC, USA). A separate model will be fitted for each of the two primary endpoints.

We will use the RR as measure of treatment effect on the relative scale for the two primary endpoints. For the composite endpoint of blood loss ≥500 mL or use of additional uterotonics, the margin has been justified as 1.2 on the odds ratio (OR) scale and 1.16 on the RR scale. Heterogeneity across centres will be assessed by using a term in the logistic model for the interaction between treatment and centres. If there is heterogeneity between the centres for any of the results, the possible causes will be explored.

The secondary binary endpoints of blood loss ≥500 mL, use of additional uterotonics, blood transfusion, manual removal of placenta, additional surgical procedures, maternal death and the composite endpoint of maternal death or severe morbidity, will be analysed using the modified ITT population and will be assessed only for conventional superiority using risk differences and relative risks with 95 % CIs estimated with the same techniques described for the main endpoints.

The secondary outcome of blood loss in millilitres will be analysed using the log transformation. This is based on the following: 1) the blood loss distribution is

positively skewed; 2) different distributions were fitted to blood loss data from a large trial [15] and the lognormal distribution was found to have a very good fit (personal communication); and 3) the lognormal distribution was used for blood loss data in the literature [13]. Therefore, a lognormal distribution will be fitted to the blood loss data and the probabilities of blood loss ≥500 mL and of ≥1,000 mL will be compared between treatments using parametric methods. The quantiles will be compared between treatments using quantile regression [17].

Trial oversight

The trial will be overseen by two committees. The Trial Steering Committee (TSC) is composed of the WHO/HRP coordination team, investigators from the 10 participating countries and five independent members with expertise in clinical, statistical and scientific disciplines. The TSC should provide oversight of the progress of the trial and ensure the trial is conducted in accordance with the principles of good clinical practice (GCP).

The Data and Safety Monitoring Committee (DSMC), with no direct involvement in the trial, will handle any ethical issues that may arise while the trial is in progress and will scrutinize two interim analyses, the first to look at safety when 5,000 participants have been recruited, and the second conducted when 15,000 women have been recruited to look at both safety and efficacy. The interim analyses will be masked to trial investigators, trial statistician, WHO, Merck for Mothers and Ferring staff, but not to DSMC members. The DSMC will be expected to provide an ongoing risk-benefit evaluation that addresses the uncertainty necessary to continue.

Discussion

PPH is one of the major contributors to maternal mortality and morbidity worldwide. Prevention of PPH is therefore of great importance in the pursuit of improved health care for women. The decision to proceed with a large, randomized controlled trial to address this unmet medical need by evaluating the effectiveness of carbetocin RTS compared to oxytocin was based on several considerations. This included the frequent concerns about the quality of oxytocin and its stability in some developing countries, the potential advantage of carbetocin RTS due to its longer half-life (than that of oxytocin), especially when administered intramuscularly, and its heat stability. This study will be conducted under conditions where both study drugs, oxytocin and carbetocin RTS, will be kept under strict refrigeration. If the trial meets its primary endpoint of non-inferiority to oxytocin, the carbetocin RTS formulation will be made available in high-burden countries at an accessible public sector price. This would have major implications for expanding access to effective care and could have a substantial impact on maternal survival.

The risk-benefit relationship was carefully considered in the planning of the trial, as was the selection of the dose of carbetocin RTS. The selected dose for the carbetocin RTS IM injection is 100 μg, the same as the dose approved for IV injection following caesarean section. The safety profile of a 100 μg dose of the carbetocin refrigerated formulation, when administered intravenously, is derived from clinical studies as well as from pharmacovigilance activities that comprise nearly 5 million women exposed. Reported AEs during clinical trials when administered by IV after caesarean section under spinal or epidural anaesthesia are headache, tremor, hypotension, flushing, nausea, abdominal pain, pruritus, anaemia, dizziness, chest pain, dyspnoea, metallic taste and vomiting. The AEs observed were of the same type and frequency as those observed with the comparator, oxytocin. In addition, efficacy and safety data on 100 μg of the carbetocin refrigerated formulation delivered intramuscularly during vaginal delivery is available from several published randomized clinical trials [11, 18, 19]. Although the population from whom these safety data are generated is different from the study population of this protocol, women undergoing caesarean section are expected to be at the same or higher risk of AEs than women having a vaginal delivery. It is therefore expected that a carbetocin RTS dose of 100 μg IM, when used in women after vaginal delivery, will be efficacious and have a safety profile that is equal to or better than the well-characterized safety profile of 100 μg IV when used in women following caesarean section.

The study has several strengths. It is a global, multicentred, randomized, double-blind, active comparator controlled study. The active comparator is oxytocin, which is the most commonly recommended drug for PPH prophylaxis and considered the current gold standard in WHO guidelines. The 10 IU dose of oxytocin was chosen as this is currently the most commonly used dose in clinical practice internationally when IM administration is practiced. Blood loss of ≥1,000 mL is a primary endpoint in this trial, as it was considered as one of the three critical endpoints (together with blood transfusion and maternal death) for the earlier 2007 WHO recommendations for PPH prevention where outcomes were rated by an independent panel [1]. We also used reliable estimates of prevalence of blood loss ≥1,000 mL under active management with oxytocin from different trials and systematic reviews. Additionally, an external DSMC has been established for the ongoing assessment of the risk-benefit ratio. One limitation of our study is that the predicted sample size makes assumptions that in reality might not hold. For example, if the efficacy of oxytocin is much better than that of carbetocin RTS, this would imply that non-inferiority is not likely to be demonstrated and the trial should be stopped for futility. If

oxytocin is just slightly better than carbetocin RTS, the predicted sample size could have been underestimated, but this is not likely given previous evidence [11].

Results of this trial will be extremely useful, particularly in tropical settings, where cold storage is difficult to achieve and maintain. Should this trial demonstrate that carbetocin RTS is non-inferior to oxytocin in preventing postpartum haemorrhage, in settings where the cold chain cannot be guaranteed, oxytocin could be replaced by carbetocin RTS as the uterotonic used during the third stage of labour. In addition, and based on the tripartite agreement signed between WHO/HRP, Merck for Mothers and Ferring Pharmaceuticals, carbetocin RTS could be available in high-burden countries at a public sector price comparable to oxytocin's price. This could have major implications for preventing PPH and a substantial impact on maternal survival worldwide.

Trial status

The trial has started recruitment in five countries. The other five countries are expected to receive regulatory authorities' approval before April 2016.

Additional files

Additional file 1: Countries ethics committees list and status of the project approval request. (DOCX 15 kb)

Additional file 2: Rationale for the choice of the non-inferiority trial the choice of the non-inferiority trial [20-22]. (DOCX 24 kb)

Abbreviations

AE: adverse event; CI: confidence interval; DSMC: Data Safety Monitoring Committee; GCP: good clinical practice; HRP: the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction; IM: intramuscular; IMP: investigational medicinal product; ITT: intention to treat; IU: international unit; IV: intravenous; mL: millilitres; PPH: postpartum haemorrhage; RHR: reproductive health and research; RR: risk ratio; RTS: room temperature stable; SAE: serious adverse event; sPPH: severe postpartum haemorrhage; TSC: Trial Steering Committee; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests. WHO/HRP is solely responsible for the trial. Merck for Mothers is providing the funding and Ferring Pharmaceuticals the carbetocin RTS. The collaboration between WHO/HRP, Merck for Mothers and Ferring Pharmaceuticals is governed by a tripartite agreement.

Authors' contributions

The protocol was written by AMG, GP and MW (WHO/HRP coordination team) with comments and contributions from HA, GC, YSC, AC, BF, SG, GJH, PL, KM, TMHN, ZQ and JPS (country investigators and members of the Trial Steering Committee). All authors contributed to the development of the trial protocol and approved the submitted manuscript.

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ORIGINAL ARTICLE

Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth

M. Widmer, G. Piaggio, T.M.H. Nguyen, A. Osoti, O.O. Owa, S. Misra, A. Coomarasamy, H. Abdel-Aleem, A.A. Mallapur, Z. Qureshi, P. Lumbiganon, A.B. Patel, G. Carroli, B. Fawole, S.S. Goudar, Y.V. Pujar, J. Neilson, G.J. Hofmeyr, L.L. Su, J. Ferreira de Carvalho, U. Pandey, K. Mugerwa, S.S. Shiragur, J. Byamugisha, D. Giordano, and A.M. Gülmezoglu, for the WHO CHAMPION Trial Group*

ABSTRACT

BACKGROUND

Postpartum hemorrhage is the most common cause of maternal death. Oxytocin is the standard therapy for the prevention of postpartum hemorrhage, but it requires cold storage, which is not available in many countries. In a large trial, we compared a novel formulation of heat-stable carbetocin with oxytocin.

METHODS

We enrolled women across 23 sites in 10 countries in a randomized, double-blind, noninferiority trial comparing intramuscular injections of heat-stable carbetocin (at a dose of 100 μg) with oxytocin (at a dose of 10 IU) administered immediately after vaginal birth. Both drugs were kept in cold storage (2 to 8°C) to maintain double-blinding. There were two primary outcomes: the proportion of women with blood loss of at least 500 ml or the use of additional uterotonic agents, and the proportion of women with blood loss of at least 1000 ml. The noninferiority margins for the relative risks of these outcomes were 1.16 and 1.23, respectively.

RESULTS

A total of 29,645 women underwent randomization. The frequency of blood loss of at least 500 ml or the use of additional uterotonic agents was 14.5% in the carbetocin group and 14.4% in the oxytocin group (relative risk, 1.01; 95% confidence interval [CI], 0.95 to 1.06), a finding that was consistent with noninferiority. The frequency of blood loss of at least 1000 ml was 1.51% in the carbetocin group and 1.45% in the oxytocin group (relative risk, 1.04; 95% CI, 0.87 to 1.25), with the confidence interval crossing the margin of noninferiority. The use of additional uterotonic agents, interventions to stop bleeding, and adverse effects did not differ significantly between the two groups.

CONCLUSIONS

Heat-stable carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 ml or the use of additional uterotonic agents. Noninferiority was not shown for the outcome of blood loss of at least 1000 ml; low event rates for this outcome reduced the power of the trial. (Funded by Merck Sharpe & Dohme; CHAMPION Australian New Zealand Clinical Trials Registry number, ACTRN12614000870651; EudraCT number, 2014-004445-26; and Clinical Trials Registry–India number, CTRI/2016/05/006969.)

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*A complete list of investigators in the WHO CHAMPION Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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Despite substantial reductions in maternal mortality, hemorrhage continues to be the largest direct cause of maternal death, accounting for 661,000 deaths worldwide between 2003 and 2009.[1] More than 70% of hemorrhagic deaths occur post partum, and most are due to uterine atony, which results from poor contraction of the uterus after childbirth. Oxytocin, the current standard therapy for the prevention of postpartum hemorrhage, has unsatisfactory real-world efficacy as a result of sensitivity to heat and quality issues such as insufficient active ingredient or impurities.[2,3] Heat-stable carbetocin, an oxytocin analogue, does not require cold-chain transport and storage; it has been shown to maintain stability over a period of 36 months at 30°C and 75% relative humidity.[4] The heat-stable formulation of carbetocin differs from the existing non–heat-stable formulation only in its excipients.

The World Health Organization (WHO) did not include a recommendation for carbetocin in its 2012 guideline regarding postpartum hemorrhage.[2] Although there have been trials of carbetocin, most of the trials involved women undergoing cesarean section, were small, were of varied quality, and used an intravenous route of administration.[5]

In 2013, the WHO was approached by Merck for Mothers (a philanthropic initiative of Merck, known outside the United States as Merck Sharpe & Dohme [MSD]) and Ferring Pharmaceuticals to explore the potential value of heat-stable carbetocin for reducing the incidence of maternal death. The WHO convened an international panel of stakeholders who identified the need for demonstration of noninferiority of heat-stable carbetocin before a change in guidance and practice could be considered. If noninferior to oxytocin, the heat-stable formulation of carbetocin would be made available in public-sector facilities of high-burden countries at an affordable and sustainable price, according to a memorandum of understanding signed by representatives of the WHO, Ferring Pharmaceuticals, and Merck. We thus performed a noninferiority trial comparing the effects of heat-stable carbetocin with those of oxytocin on postpartum hemorrhage after vaginal birth.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted an international, randomized, double-blind, active-controlled, noninferiority trial, the Carbetocin Haemorrhage Prevention (CHAMPION) trial, comparing heat-stable carbetocin with oxytocin for the prevention of postpartum hemorrhage during the third stage of labor in women giving birth vaginally at 23 hospitals (sites) in 10 countries — Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and the United Kingdom — between July 7, 2015, and January 30, 2018. The trial protocol (available with the full text of this article at NEJM.org) has been published previously.[6] The trial protocol was approved by the relevant ethics committees and regulatory agencies in each country, by the research proposals review panel of the Special Program of Research in Human Reproduction (HRP) that is based at the WHO, and by the WHO Ethics Review Committee.

HRP oversaw the conduct of the trial, which was performed in accordance with Good Clinical Practice guidelines.[7] An external data and safety monitoring committee provided independent oversight and reviewed two interim analyses: the first analysis was to evaluate safety when 5000 participants had been recruited, and the second was to evaluate safety and efficacy when 15,000 participants had been recruited. The interim analyses were blinded to everyone except the members of the data and safety monitoring committee. On both occasions, the data and safety monitoring committee recommended continuation of the trial.

Trial initiation, monitoring, and closure and safety monitoring at the trial sites were provided by IQVIA (formerly Quintiles IMS–Quintiles). Centro Rosarino de Estudios Perinatales in Rosario, Argentina, provided assistance with data management, including preparation of the trial online data-entry system, electronic case-record forms, and data monitoring and cleaning. Statistika Consultoria in Campinas, Brazil, provided statistical assistance. The trial protocol, statistical analysis plan, and the manuscript were written by HRP staff, the trial statistician, independent steering committee members who were not WHO staff or site investigators, and the site principal investigators.

The trial was supported by MSD, through the MSD for Mothers Program, an initiative of Merck; MSD had no commercial interest in the investigational drug. Heat-stable carbetocin was provided by Ferring Pharmaceuticals and oxytocin by Novartis free of charge. Novartis had no other role in the trial. MSD and Ferring Pharmaceuticals provided input into the protocol and could provide

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comments on the manuscript, although there was no obligation on the part of the team to incorporate them. No company had the right to final approval of the manuscript or to control the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of this report to the to the protocol.

TRIAL PARTICIPANTS AND INTERVENTIONS

Women who expected to give birth vaginally and who had a singleton pregnancy and cervical dilatation of 6 cm or less were eligible. Women were not eligible if they were in an advanced stage of labor (cervical dilatation >6 cm); were too distressed to provide informed consent; had known allergies to carbetocin, oxytocin homologues, or excipients; or had a serious cardiovascular disorder, serious hepatic or renal disease, or epilepsy. All the participants provided written informed consent.

Women underwent randomization when vaginal birth was imminent. Women were randomly assigned to receive a single intramuscular injection of either heat-stable carbetocin at a dose of 100 μg or oxytocin at a dose of 10 IU. Immediately after the birth of the baby, the drug was administered and the management of the third stage of labor was conducted as recommended in the WHO guidelines.[2] Once the umbilical cord was clamped and cut, a plastic drape for blood collection (BRASSS-V Drape) was placed under the woman's buttocks. Blood was collected for 1 hour or for 2 hours if the bleeding continued beyond 1 hour. The drape with the blood was then weighed by a digital scale, with the weight recorded in grams and then converted to volume (milliliters) after the weight of the drape was subtracted at the analysis stage.[8]

Participation in the trial ended at discharge from the facility, transfer of the woman to a higher care unit, or death. Information on serious and other adverse events was collected from the time of informed consent until the event resolved.

Heat-stable carbetocin and oxytocin were both supplied in 1-ml ampules in consecutively numbered treatment packs that were arranged in dispensers. The ampules, trial packs, and dispensers were identical in shape, size, and weight to ensure that investigators were unaware of the individual treatment assignments. Although carbetocin was heat stable and did not require cold storage, the dispensers were kept in cold storage (2 to 8°C) to give oxytocin maximum efficacy and to maintain double-blinding.

The random-assignment sequence was generated at the WHO with the use of computer-generated random numbers. Randomization was stratified according to country with the use of permuted blocks of 10, with an assignment ratio of 1:1. Assignment was performed by opening the consecutively numbered treatment pack in the dispenser.

PRIMARY AND SECONDARY OUTCOMES

There were two primary outcomes. The first was a composite outcome of the proportion of women with blood loss of at least 500 ml or the use of additional uterotonic agents at 1 hour and up to 2 hours for women who continued to bleed after 1 hour. This outcome was deemed to be sufficient and appropriate for submission for regulatory approval after discussion with the U.K. Medicines and Healthcare Products Regulatory Agency. The second primary outcome was the proportion of women with blood loss of at least 1000 ml at 1 hour and up to 2 hours for women who continued to bleed after 1 hour. This outcome had been used in earlier WHO guidelines regarding the prevention of postpartum hemorrhage. For these two primary outcomes, a noninferiority hypothesis was used.

Secondary outcomes included other measurements related to blood loss, such as the use of additional uterotonic agents, other interventions to stop bleeding (Table S1 in the Supplementary Appendix, available at NEJM.org), and expected adverse effects, including chest pain, flushing, abdominal pain, and vomiting. For secondary outcomes, a superiority hypothesis was used.

STATISTICAL ANALYSIS

Details of the statistical analysis have been published previously[6] and are available with the trial protocol. For the primary outcome of blood loss of at least 500 ml or the use of additional uterotonic agents, we set a noninferiority margin of 1.16 on the relative scale to preserve at least 82% of the effect of oxytocin over placebo, assuming the prevalences from a systematic review (15 to 20% with oxytocin and 29 to 37% with placebo).[9] For the primary outcome of blood loss of at least 1000 ml, we set the noninferiority margin to preserve at least 75% of the effect of oxytocin over placebo, assuming a prevalence of this outcome of 2% with oxytocin[10] and 3.84% with placebo

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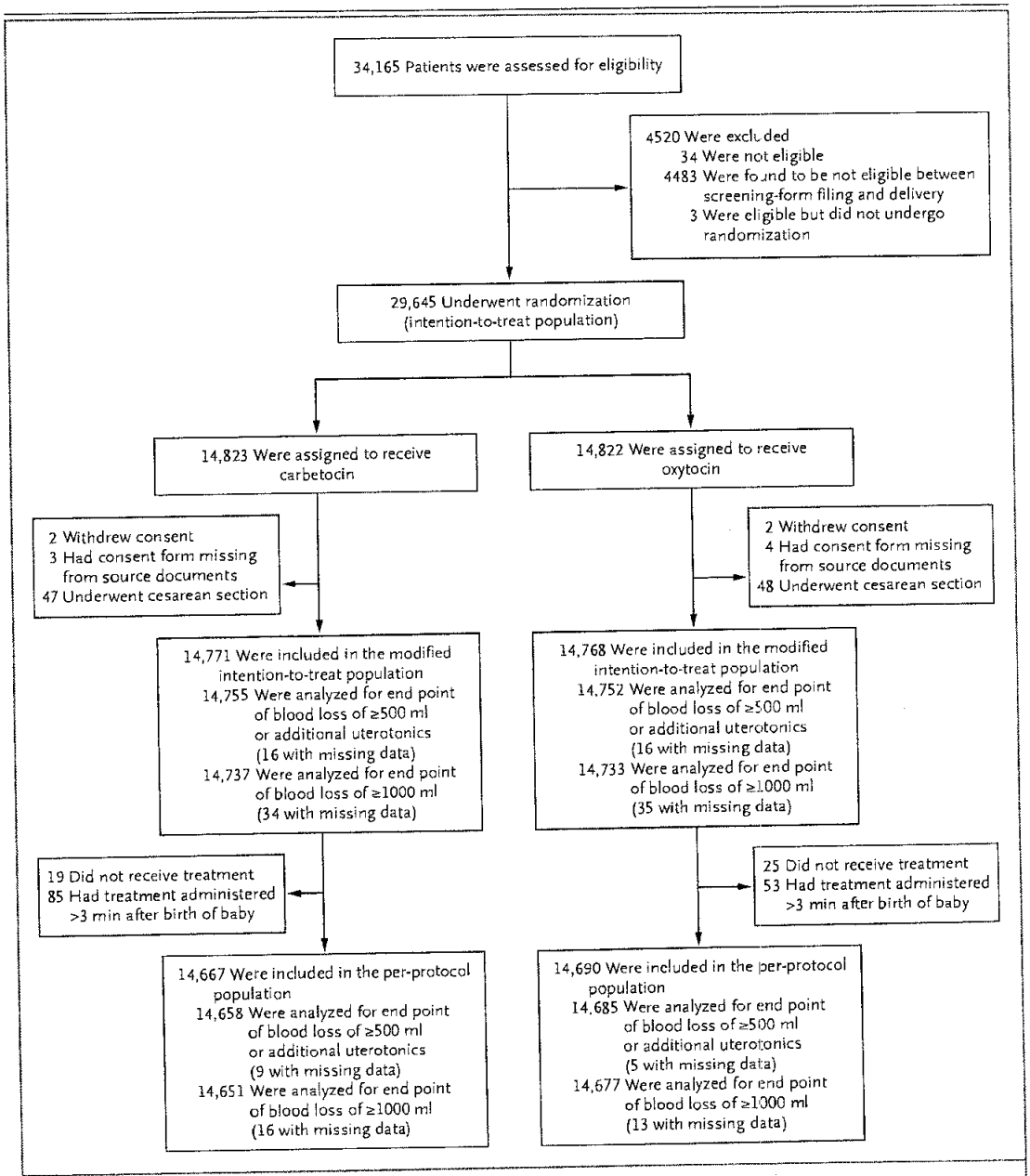

Figure 1. Trial Profile and Modified Intention-to-Treat and Per-Protocol Populations.

Informed consent was sought at hospital admission (see the protocol).

(derived from rates with expectant management in a systematic review).[11] Preserving 75% of 1.84 percentage points (i.e., 3.84% − 2%) gave a margin on the absolute scale of 0.46 percentage points (or 2.46÷2=1.23 on the relative scale), assuming a 2% prevalence with oxytocin.

To show the noninferiority of heat-stable carbetocin as compared with oxytocin within a margin of 1.23 on the relative scale, with 80% power and at a significance level of 2.5%, we calculated that 29,082 women would need to be enrolled, assuming an equal prevalence of blood loss of at least 1000 ml of 2% in each treatment group. We assumed a 3% rate of loss to follow-up, which resulted in an estimated sample size of 30,000. This sample size provided the trial with more than

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Table 1. **Characteristics of Women at Trial Entry and of Women and Babies at Birth (Modified Intention-to-Treat Population).***

Characteristic	Carbetocin (N=14,771)	Oxytocin (N=14,768)
Age — yr		
Median	25	25
Interquartile range	22–30	22–30
Nulliparous — no. (%)	6,424 (43.5)	6,457 (43.7)
Gestational age — wk		
Median	39	39
Interquartile range	38–40	38–40
Labor induced — no. (%)	2,064 (14.0)	2,032 (13.8)
Labor augmented — no. (%)	6,891 (46.7)	6,948 (47.0)
Instrument-assisted vaginal birth — no. (%)	568 (3.8)	580 (3.9)
Perineal trauma leading to suture — no. (%)	9,207 (62.3)	9,243 (62.6)
Birth weight — g		
Median	3090	3080
Interquartile range	2780–3420	2800–3400
Baby alive — no. (%)	14,581 (98.7)	14,584 (98.8)
Previous cesarean section — no./total no. (%)	433/8347 (5.2)	459/8311 (5.5)
Previous postpartum hemorrhage — no./total no. (%)	121/8347 (1.4)	128/8311 (1.5)

* The modified intention-to-treat population included all the participants who underwent randomization except those who withdrew consent, underwent cesarean section, or had another reason for withdrawal. Data regarding whether labor was induced or augmented or whether there was perineal trauma leading to suture were missing for one woman in the carbetocin group. There were no significant ($P<0.05$) differences between the two groups.

99% power for the outcome of blood loss of at least 500 ml or the use of additional uterotonic agents. The sample size was calculated for different scenarios as specified in the protocol. For the scenario of a prevalence of 1.5% for the outcome of blood loss of at least 1000 ml, the margin on the relative scale was 1.31. We defined a priori the number needed to harm (i.e., the number of women who would need to be treated with carbetocin instead of oxytocin to result in one woman with blood loss of ≥1000 ml) for noninferiority as an absolute measure and stated that noninferiority would be shown if the number needed to harm was 217 or more.

We present the primary-outcome results with adjustment for multiple comparisons as a complementary analysis. However, our conclusions are based on the unadjusted results.

Analyses were planned according to the modified intention-to-treat and per-protocol populations. The modified intention-to-treat population included all the participants who underwent randomization except those who withdrew consent, those whose consent form was missing from source documents, and those who underwent cesarean section. The per-protocol population included all the participants who received the assigned treatment within 3 minutes after delivery. To conclude that heat-stable carbetocin was noninferior to oxytocin, we required that noninferiority be shown in both the modified intention-to-treat and per-protocol analyses.

We used the Mantel–Haenszel method to calculate summary relative-risk estimates and common risk (proportion) differences for tables of the type country by trial group by binary outcome. The confidence intervals were obtained by the Wald method, and the P value was from the Mantel–Haenszel general association statistic. This approach differed from the modeling approach with the use of logistic regression as planned in the protocol, because the results from logistic regression were not reliable with scarce data. Missing values were not imputed. We planned to use com-

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Table 2. Primary and Secondary Outcomes.*

Outcome	Carbetocin (N = 14,771)	Oxytocin (N = 14,768)	Relative Risk (95% CI)	Risk Difference (95% CI)
	number (percent)			*percentage points*
Primary outcomes in the modified intention-to-treat population				
Blood loss ≥500 ml or use of additional uterotonic agents†	2135 (14.5)	2122 (14.4)	1.01 (0.95 to 1.06)	0.09 (−0.68 to 0.87)
Blood loss ≥1000 ml‡	223 (1.51)	214 (1.45)	1.04 (0.87 to 1.25)	0.06 (−0.21 to 0.33)
Primary outcomes in the per-protocol population				
No. of women	14,667	14,690		
Blood loss ≥500 ml or use of additional uterotonic agents†	2107 (14.4)	2098 (14.3)	1.01 (0.96 to 1.06)	0.12 (−0.66 to 0.90)
Blood loss ≥1000 ml‡	222 (1.5)	212 (1.4)	1.05 (0.88 to 1.27)	0.08 (−0.20 to 0.35)
Maternal secondary outcomes in the modified intention-to-treat population				
Blood loss ≥500 ml§	1327 (9.0)	1343 (9.1)	0.99 (0.92 to 1.06)	—
Use of additional uterotonic agents until 2 hr¶	1339 (9.1)	1304 (8.8)	1.03 (0.96 to 1.10)	—
Use of additional uterotonic agents‖	1533 (10.4)	1528 (10.4)	1.00 (0.94 to 1.07)	—
Blood transfusion	229 (1.6)	198 (1.3)	1.16 (0.96 to 1.4)	—
Manual removal of placenta	79 (0.5)	95 (0.6)	0.83 (0.62 to 1.12)	—
Additional surgical procedures**	159 (1.1)	138 (0.9)	1.15 (0.92 to 1.44)	—
Maternal death	4 (<0.1)	2 (<0.1)	2.00 (0.37 to 10.92)	—
Maternal death or severe complication††	26 (0.2)	23 (0.2)	1.13 (0.65 to 1.98)	—
Newborn secondary outcomes in the modified intention-to-treat population				
No. of live births	14,581	14,584		
Newborn death‡‡	49 (0.3)	47 (0.3)	1.04 (0.7 to 1.55)	—
Apgar score <7 at 5 min	218 (1.5)	229 (1.6)	0.95 (0.79 to 1.14)	—
Newborn resuscitation	812 (5.6)	812 (5.6)	1.00 (0.91 to 1.10)	—
Mechanical ventilation	172 (1.2)	164 (1.1)	1.05 (0.85 to 1.30)	—

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* The modified intention-to-treat population included all the participants who underwent randomization except those who withdrew consent, those whose consent form was missing from the source documents, and those who underwent cesarean section. The per-protocol population included all the participants who received the assigned treatment within 3 minutes after delivery. Analyses were based on available outcome data. Missing values were not included in the calculations, and the denominator excludes missing values. The relative risks are for the comparison of heat-stable carbetocin with oxytocin. Confidence intervals were not adjusted for multiple comparisons for the secondary outcomes, with the use of the false-discovery-rate approach, were greater than 0.90.

† This outcome was defined as blood loss of at least 500 ml or the use of additional uterotonic agents at 1 hour and up to 2 hours in women who continued to bleed after 1 hour. In the modified intention-to-treat population, data were missing for 32 women (16 in each group). P=0.81 for superiority in the modified intention-to-treat population. In the per-protocol population, data were missing for 14 women (9 in the carbetocin group and 5 in the oxytocin group). P=0.76 for superiority in the per-protocol population.

‡ This outcome was defined as blood loss of at least 1000 ml at 1 hour and up to 2 hours for women who continue to bleed after 1 hour. In the modified intention-to-treat population, data were missing for 69 women (34 in the carbetocin group and 35 in the oxytocin group). In the per-protocol population, data were missing for 29 women (16 in the carbetocin group and 13 in the oxytocin group).

§ Data were missing for 69 women (34 in the carbetocin group and 35 in the oxytocin group).

¶ This outcome was defined as the use of additional uterotonic agents at 1 hour and up to 2 hours for women who continued to bleed after 1 hour. Data were missing for one woman in the carbetocin group.

‖ This outcome was defined as the use of additional uterotonic agents until discharge. Data were missing for one woman in the carbetocin group.

** Additional surgical procedures were defined as suturing of cervix or high vaginal tear, exploration of the uterine cavity while the woman was under general anesthesia, uterine or hypogastric ligation, uterine compression suture, or hysterectomy.

†† Maternal severe complication was defined as admission to the intensive care unit, hysterectomy, blood loss of at least 2 liters, or uterine inversion. Data were missing for 69 women (34 in the carbetocin group and 35 in the oxytocin group).

‡‡ Newborn death was assessed until discharge among babies born alive.

plete-case analysis because missing values for primary outcomes were expected to be very few and balanced between groups. As a complementary analysis, a log-normal distribution was fitted to the blood-loss data, and the estimated probabilities of blood loss of at least 500 ml and of at least 1000 ml were compared between treatments with the use of relative risk and the bootstrap technique to obtain confidence intervals for the relative risk. Because this parametric method used all the blood-loss data (instead of dichotomizing), it was expected to improve efficiency in terms of the precision of the estimates (see the Supplementary Appendix).

The secondary outcomes were assessed only for superiority, with the use of relative risks with 95% confidence intervals that were estimated with the same techniques as described for the primary outcomes. Because the statistical analysis plan did not include a provision for correcting the confidence intervals for multiple comparisons, the widths of the confidence intervals were not adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. Analyses were performed with SAS software, version 9.4 (SAS Institute), and JMP 13Pro software (JMP).

RESULTS

PARTICIPANTS

We recruited 29,645 women in 10 countries. The trial profile and populations are shown in Figure 1. Cesarean birth after randomization occurred in 47 women (0.3%) in the carbetocin group and in 48 (0.3%) in the oxytocin group. Outcomes were missing for the first primary outcome for 16 participants in each group and for the second primary outcome for 34 participants (0.2%) in the carbetocin group and for 35 (0.2%) in the oxytocin group. The characteristics at baseline and the birth outcomes were similar in the two groups (Table 1).

PRIMARY OUTCOMES

The primary outcome of blood loss of at least 500 ml or the use of additional uterotonic agents occurred in 14.5% of the women in the carbetocin group and in 14.4% of those in the oxytocin group (relative risk, 1.01; 95% confidence interval [CI], 0.95 to 1.06; 95% CI adjusted for multiple comparisons owing to having two primary outcomes, 0.94 to 1.07; P<0.001 for noninferior-

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ity), a result that was consistent with noninferiority at the prespecified margin of 1.16. Superiority was not shown (P=0.81).

The second primary outcome, blood loss of at least 1000 ml, occurred in 1.51% of the women in the carbetocin group and in 1.45% of those in the oxytocin group (relative risk, 1.04; 95% CI, 0.87 to 1.25; adjusted 95% CI, 0.85 to 1.28; P=0.03 for noninferiority). The nonsignificant results for the second primary outcome were close to showing noninferiority but did not, probably owing to lack of power.[12] On the absolute scale, the upper limit of the 95% confidence interval for the risk difference was 0.33 percentage points (Table 2), which was below the prespecified margin of 0.46 percentage points, and the corresponding number needed to harm was 303 (100÷0.33), which was higher than the preset value of 217 (100÷0.46) for indicating noninferiority.

In analyses fitting a log-normal distribution, followed by bootstrap techniques to obtain confidence intervals for the relative risk, the relative risk for the outcome of blood loss of at least 1000 ml that was associated with heat-stable carbetocin, as compared with oxytocin, was 1.00 (95% CI, 0.89 to 1.13), which was within the noninferiority margin of 1.23. We also performed a post hoc analysis using a composite outcome of blood loss of at least 1000 ml or the use of additional uterotonic agents; the relative risk was 1.01 (95% CI, 0.95 to 1.09).

Results in the modified intention-to-treat and per-protocol populations did not differ materially from each other. In the per-protocol population, results for the outcome of blood loss of at least 500 ml or the use of additional uterotonic agents were consistent with the noninferiority of carbetocin (relative risk vs. oxytocin, 1.01; 95% CI, 0.96 to 1.06). For the outcome of blood loss of at least 1000 ml, the upper limit of the 95% confidence interval (1.27) was above the noninferiority margin of 1.23 (Table 2).

SECONDARY OUTCOMES AND ADVERSE EFFECTS

There were no differences at the 5% level of significance between groups in the rates of the secondary outcomes (Table 2). There were six maternal deaths (four in the carbetocin group and two in the oxytocin group). In the carbetocin group, deaths were due to uterine atony, retained placenta with hemorrhage, sepsis, and placental abruption causing intrapartum and postpartum hemorrhage (in one participant each). In the oxytocin group, deaths were due to amniotic fluid embolism and to placental abruption causing intrapartum and postpartum hemorrhage (in one participant each). Among the women who received treatment (safety population), the frequencies of the expected adverse effects did not differ significantly between the two groups (Table 3).

In the safety population, the percentages of women with at least one unanticipated adverse event were 4.9% in the carbetocin group and 4.7% in the oxytocin group. The percentages of women who had at least one serious adverse event were 0.7% in the carbetocin group and 0.6% in the oxytocin group.

DISCUSSION

In this multicenter, double-blind, randomized trial, we found that the intramuscular administration of 100 μg of heat-stable carbetocin was noninferior to the administration of 10 IU of oxytocin for the prevention of postpartum hemorrhage after vaginal birth, when the outcome was defined as blood loss of at least 500 ml or the use of additional uterotonic agents. For the second primary outcome of blood loss of at least 1000 ml, noninferiority was not shown; the upper 95% confidence limit exceeded the noninferiority margin.

We calculated our sample size on the basis of literature describing a prevalence of 2% of blood loss of at least 1000 ml.[10] However, in our trial, this outcome occurred in 1.51% of the participants in the carbetocin group and in 1.45% of those in the oxytocin group. Despite the fact that this was a very large, randomized trial investigating the prevention of postpartum hemorrhage, it was underpowered for the outcome of blood loss of at least 1000 ml. In contrast to our primary prespecified noninferiority analysis for this outcome, the log-normal analysis, which had the advantage of taking into account all the blood-loss measures instead of dichotomizing them, provided narrower 95% confidence intervals that were entirely within the prespecified noninferiority margin of 1.23. We found no significant differences between the two groups with regard to secondary outcomes or adverse effects.

The present trial provides a large-scale noninferiority evaluation of heat-stable carbetocin against oxytocin as the standard therapy. Previous studies have been small, with likely biases and differences

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in doses, administration routes, and study populations. Five previous trials compared carbetocin with oxytocin.[5] Four of these trials involved women with cesarean births only, and the oxytocin doses that were used ranged from an intravenous bolus of 2.5 IU or 5 IU to the infusion of 10 IU over a period of 2 hours. These trials were not designed as noninferiority trials.

The trial was motivated by the proven heat-stability profile of heat-stable carbetocin.[4] Although the United Nations Commission for Life-Saving Commodities recommends that oxytocin be supplied and stored between 2°C and 8°C to ensure efficacy,[13] in many settings oxytocin is still stored at room temperature, which leads to degradation and loss of efficacy in approximately one third of ampules.[3] In the present trial, we used high-quality oxytocin and stored both the heat-stable carbetocin and the oxytocin between 2°C and 8°C to maintain blinding and to provide oxytocin the best chance of efficacy. Thus, the present trial may underestimate the benefit that would be expected with the use of heat-stable carbetocin in low-income and middle-income countries. Avoiding the need for a cold chain will enable lower-cost transport and storage as well as reduce the waste associated with heat-exposure–related degradation and loss of active ingredient. Within the labor-ward environment, eliminating a need for cold storage will facilitate easier access to the drug for patient care.

In conclusion, this multicenter trial showed the noninferiority of heat-stable carbetocin, as compared with oxytocin, for the primary outcome of blood loss of at least 500 ml or the use of additional uterotonic agents. Noninferiority was not shown for the primary outcome of blood loss of at least 1000 ml; however, the trial was underpowered for this outcome. There were no significant differences between the two groups in other measures of bleeding or in adverse effects. These data inform care of women in parts of the world where a lack of heat stability is a barrier to the effective prevention of postpartum hemorrhage.

Table 3. Side Effects in the Safety Population.*

Side Effect	Carbetocin (N=14,754)	Oxytocin (N=14,743)	Risk Difference (95% CI)
	no. of women with event (%)		*percentage points*
Chest pain	13 (0.09)	6 (0.04)	0.05 (−0.01 to 0.11)
Flushing	5 (0.03)	4 (0.03)	0.01 (−0.03 to 0.05)
Abdominal pain	63 (0.43)	56 (0.38)	0.05 (−0.10 to 0.19)
Vomiting	33 (0.22)	27 (0.18)	0.04 (−0.06 to 0.14)

* The safety population included all the participants who received treatment. The risk difference was adjusted for country.

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APPENDIX

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SPECIAL COLLECTION

ORIGINAL ARTICLE *HEAT-STABLE CARBETOCIN, PUBLIC-PRIVATE PARTNERSHIP*

Introduction of Heat-Stable Carbetocin through a Public-Private Partnership Model: A Retrospective Study to Determine Feasibility and Optimal Use in Public Health Settings in India

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ABSTRACT

Background and Objective: The optimal use of oxytocin for preventing postpartum hemorrhage (PPH) faces challenges in many low-middle income countries (LMICs) owing to its storage and transportation prerequisites. We demonstrated Heat-Stable Carbetocin (HSC) for PPH prevention through an innovative Public-Private Partnership (PPP) model in 15 public health facilities of the Dewas District of Madhya Pradesh (MP) state in India. This study evaluates the feasibility and appropriate utilization of HSC in public health settings.

Methods: We analyzed facility-level data collected between August 2022 and July 2023 from selected 15 health facilities, where HSC was introduced. Prior to the introduction of HSC, all healthcare providers received training on Active Management of the Third Stage of Labor (AMTSL), use of HSC, and recording and reporting procedures. The supply of HSC in health facilities was ensured, and a robust mechanism was set up to monitor the progress.

Results: A total of 18,497 women were admitted for delivery in the 15 selected facilities. Uterotonic administration within one minute of delivery was almost universal (99.9%). No instance was recorded of using HSC either for induction of labor or management of PPH. In 636 cases (3.43%), HSC was not given for PPH prevention. Pearson's chi-square test was conducted to assess the relationship between HSC usage and the health facility's level. The HSC use was significantly higher in First Referral Unit (FRU) facilities compared to non-FRUs ($p < 0.001$). Moreover, the administration of HSC within one minute of delivery was also more prevalent in FRU facilities compared to non-FRUs ($p < 0.001$). The PPH incidence and case referral rates noted in this study were 0.7% and 16.7%, respectively, with no reported adverse drug events or deaths.

Conclusion and Global Health Implications: Our study suggests the safe and appropriate use of HSC within India's public health system.

Keywords: Postpartum Hemorrhage, Heat-Stable Carbetocin, Uterotonic, Active Management of Third Stage of Labor, Maternal Health

INTRODUCTION

Background of the Study

Childbirth is the most crucial time when pregnant women and newborn babies are at the highest risk of morbidity and mortality. Nearly 46% of all maternal deaths and 40% of neonatal deaths

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usually occur during labor or the first 24 hours after birth. Postpartum hemorrhage (PPH), hypertension, sepsis, and obstructed labor are the major causes of maternal deaths.[1] Most of these deaths can be prevented by conducting evidence-based practices during the period around childbirth.

The PPH is a leading cause of maternal death globally, accounting for about one-quarter of all maternal deaths. India, with its high maternal mortality rate (97 deaths per 10,000 live births from 2018 to 2020)[2] is no exception, as 38% of maternal deaths are due to PPH.[3]

Oxytocin, a World Health Organization (WHO) recommended uterotonic drug is one of the most widely used drugs for preventing and managing PPH. Oxytocin has a short half-life of 1–6 minutes,[4] making it a suitable drug for safely inducing or augmenting labor in specific clinical scenarios.[5] However, oxytocin is not without its challenges. Oxytocin is heat-sensitive and must be stored at 2–8 degrees Celsius,[4] which is difficult to maintain in many low- and middle-income countries (LMICs) like India because of their insufficient cold chain capacity. As a result, studies have shown that much of the oxytocin available in LMIC markets like India either does not meet drug quality standards or is stored improperly.[6–8]

In response to global interest in developing a heat-stable alternative to oxytocin for preventing PPH, a new drug, Heat-Stable Carbetocin (HSC), has been shown to prevent PPH effectively.[9–11] Unlike oxytocin, HSC is stable at 30 degrees Celsius, which is advantageous in areas without adequate cold chain capacity.[9] This drug is new to the market and has been registered recently in India, and injectable HSC (100 μg/mL) was added to the WHO's Model List of Essential Medicines in 2021.[12] At the same time, WHO has recommended HSC in contexts where the quality of oxytocin cannot be guaranteed.[4] HSC is contraindicated for inducing and augmenting labor due to its long half-life of 40 minutes.[4,5] Oxytocin and HSC pose unique challenges, particularly in India, where misuse of oxytocin is rampant and there is a risk of inappropriate HSC use.[13]

A recent study from India showed that HSC prevents more disability-adjusted life years (DALYs) and reduces costs to the public healthcare system of India.[14] In 2020, the Drug Controller General of India (DGCI) approved the use of HSC for preventing PPH, in alignment with WHO recommendations. However, no studies have been conducted so far to test the feasibility and optimal use of HSC in the existing public health system. Further research is imperative to ensure the safe and appropriate utilization of HSC to guide policymakers before its widespread adoption as an alternative to oxytocin for PPH prevention, particularly in settings where oxytocin quality may be questionable.

Under the leadership of the National Health Mission (NHM) of the State of Madhya Pradesh (MP) in India, a public-private partnership (PPP) was forged through the United States Agency for International Development's (USAID) India-awarded Systems Approach for Maternal, Newborn, and Child Health (MNCH) focusing on Vulnerable Geographies (SAMVEG) project. A consortium partnership was formed, including IPE Global Limited, DIMAGI, Inc., World Health Partners, and John Snow India Private Limited, to demonstrate an innovative model using HSC as an entry point for strengthening active management of the third stage of labor (AMTSL). Ferring Pharmaceutical, the manufacturer of HSC, was also engaged in selected health facilities for its commitment to supply HSC. The key steps involved in the development and implementation of HSC model is presented as Figure 1.

Study Objectives

The objectives of the study were to (1) understand the feasibility of introducing HSC through an innovative PPP model in the First Referral Unit (FRU) and non-FRU-level public health facilities; (2) understand the clinical practices for prophylactic use of HSC; and (3) understand the factors that enable the appropriate use of uterotonics in public health settings.

Specific Aim

The study aimed to assess the acceptability and feasibility of introducing the HSC through a PPP model, ascertain its appropriate use, and derive learnings for its possible scale-up across similar settings. Additionally, the study also aimed to examine the key factors that facilitate or restrict the appropriate utilization of HSC in public health systems, as per WHO recommendations.

METHODS

This manuscript followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) recommendations for the reporting of study findings. Fifteen public health facilities out of 32 in the Dewas District of MP were purposively selected, based on the monthly delivery load and their ability to provide comprehensive emergency obstetric and newborn care (CEmONC) services to demonstrate the implementation of this innovative model. A detailed situational analysis of health facilities was conducted to assess the status of AMTSL practices, availability of human resources, training, uterotonics, cold chain processes, and recording and reporting of service data. A specially constituted Technical Advisory Group (TAG) developed the training materials and job aids per the existing country

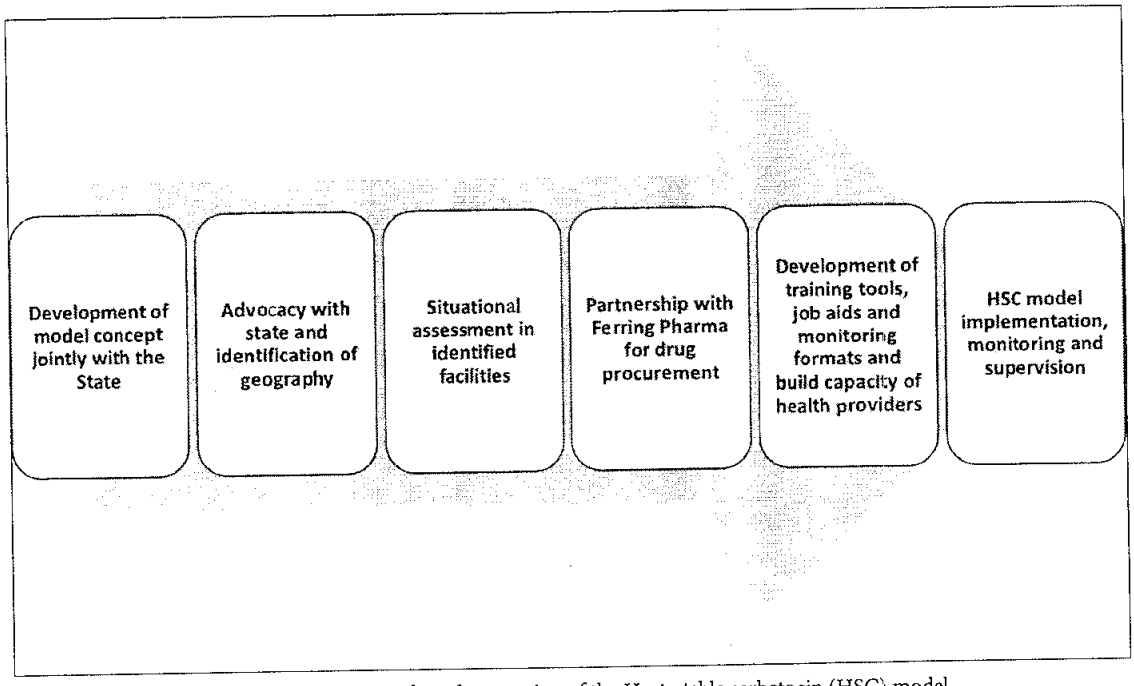

Figure 1: Key steps involved in the development and implementation of the Heat-stable carbetocin (HSC) model.

guidelines, focusing on the appropriate use of HSC, including contraindications to its administration. Local language adaptation was done after obtaining State Government approvals for the training materials. Based on the findings of the situational analysis, one-day training on strengthening care around AMTSL, including appropriate use of HSC, was provided to healthcare providers, and the provision of posters and job aids was also ensured for a practical and standardized implementation of the model. The supply of HSC in all the selected health facilities was secured, and a robust monitoring and supportive supervision mechanism was set up to monitor the project's progress.

Study Design and Settings

This was a retrospective study wherein we analyzed facility-level data collected between August 2022 and July 2023 from the 15 selected health facilities in the Dewas district of MP, where HSC was introduced through a PPP model. The health facilities comprised two FRU-level facilities, that is, one district hospital and one community health center (CHC), along with 13 non-FRU facilities: three CHCs, eight Primary Health Centers (PHCs), and two Health and Wellness Centers (HWCs).

Data Collection

At the facility level, usually a standardized paper-based delivery register and a case sheet are used for each delivery. Based on the findings of the situational analysis, new fields in the case sheet and delivery register were added to record the timing of uterotonic administration (within one minute of delivery). To ensure data accuracy, all service providers received training on AMTSL and the appropriate use of HSC as well as recording and reporting procedures before initiating the intervention. HSC was provided monthly using the state drug distribution system, and existing recording formats were adapted to include the uterotonic administration time. A nurse mentor provided supportive supervision and collected information related to the model once every month from each of the 15 facilities.

At the end of each month, facility staff gathers facility-level data from a paper-based delivery register. This data is then compiled using Microsoft Excel (Office 365) before being shared with the district nodal person based at the NHM for district-level compilation and analysis.

The monthly facility-wise delivery data compiled between August 2022 and July 2023 from all 15 health facilities were used to perform the analysis in this study.

Study Variables

The key outcomes of interest included: (1) the number of deliveries conducted in the facilities, deliveries where HSC was used, (2) the number of cases of HSC administration within one minute of delivery, (3) cesarean section deliveries that received HSC, and (4) patients given uterotonics for

PPH management disaggregated by drug type. No personal identifiers of the beneficiaries delivered to health facilities were collected. Complete data analysis and interpretation were done in an aggregated form.

Statistical Analysis

We performed health facility-level analysis using Microsoft Excel (Office 365), and the results are reported in aggregated form in terms of frequencies and proportions. Additionally, the association between HSC use for PPH prevention and level of health facility was calculated and compared for statistical significance using Pearson's chi-square test.

Ethical Approval

We received administrative authorization from the NHM of Madhya Pradesh before conducting this analysis. Additionally, this study was reviewed and approved by the International Institute of Health Management Research (IIHMR), New Delhi.

RESULTS

The model was implemented in 15 of the existing 32 facilities providing delivery services, including two facilities providing CEmONC services, where 80% of deliveries were reported in the previous year. The project activities are currently ongoing. However, we analyzed 12 months of project implementation data of the study covering the period from August 2022 to July 2023.

Main Variable Results

A total of 88 service providers, including 70 nursing officers, were trained by leveraging the state government's logistics and trainers. Implementation one year after the model's launch by the State Government and supply of HSC revealed that, as per the records of the delivery point, a total of 18,497 women were admitted for care at childbirth in the 15 implementing facilities. In addition, 543 pregnant women (2.9%) who had transit deliveries before they could reach the delivery points were also managed. However, these were not included in the analysis.

Uterotonic administration within one minute of delivery was almost universal (98.8%). No instance was recorded of using HSC either for induction of labor or management of PPH. Facility-wise uterotonic administration and mode of delivery are shown in Table 1.

In 636 cases (3.43%), HSC was not given for PPH prevention. PPH incidence documented in this study was 0.7%, with 126 reported PPH cases. A higher incidence was reported from non-FRU facilities (1.4%), and no PPH was reported in cesarean births. Uterine atony (69%) was the most reported cause of PPH, followed by birth trauma (23.8%). No case was reported where a surgical intervention was undertaken. At the same time, overall compliance with evidence-based monitoring practices with partograph (95.3%) and early initiation of breastfeeding (90.6%) was seen. The referral rate in PPH cases was 16.7%, and no death was reported, as shown in Table 2.

Table 1: Status of uterotonic use for postpartum hemorrhage (PPH) prevention and its mode of delivery.

Practices	Type of Facility		TOTAL
	FRU	non-FRU	
Number of facilities	2	13	15
Total Deliveries	11,536	6961	18,497
Vaginal Delivery	8270 (71.7%)	6961 (100%)	15,231 (82.3%)
Caesarean Delivery	3266 (28.3%)	0	3266 (17.7%)
Uterotonic used	11,529 (99.9%)	6952 (99.4%)	18,481 (99.9%)
Uterotonic used within one minute of delivery	11,523 (99.9%)	6745 (96.9%)	18,268 (98.8%)
HSC Used	11,289 (97.9%)	6572 (94.4%)	17,861 (96.6%)
Oxytocin Used	240 (2.1%)	380 (5.5%)	620 (3.4%)
HSC administered within one minute of delivery	11,283 (99.9%) N = 11,289	6365 (96.9%) N = 6572	17,648 (98.8%) N = 17861
Oxytocin administered within one minute of delivery	223 (92.9%) N = 240	316 (83.2%) N = 380	539 (86.9%) N = 620

FRU: First referral unit, HSC: Heat-stable carbetocin, N: Number of cases wherein HSC was used.

The Person's chi-square test was employed to assess the association between the use of HSC for PPH prevention and the type of health facility. The results indicate a significant association, with notably higher utilization of HSC for preventing PPH observed in FRU-level facilities compared to non-FRU facilities ($p < 0.001$). Additionally, the administration of HSC within one minute of delivery was also significantly more frequent in FRU facilities compared to non-FRU facilities ($p < 0.001$) [Table 3]. A total of 12 structured district-level review meetings (one per month) were conducted by the district authorities to oversee the consistent availability of the HSC drug and address any challenges, including adverse drug events, encountered

Table 2: Status of postpartum hemorrhage (PPH) cases and their management at selected health facilities.

PPH	Type of Facility		Total
	FRU	non-FRU	
Number of cases	25 (0.2%)	101 (1.4%)	126 (0.7%)
HSC Used	N = 11,536	N = 6961	N = 18,497
Oxytocin Used	23 (0.2%)	80 (1.2%)	103 (0.6%)
	(N = 11,289)	N = 6572	N = 17,861
	2 (0.8%)	21 (5.5%)	23 (3.7%)
	N = 240	N = 380	N = 620
Atony	22(88%)	65 (64.4%)	87 (69%)
Birth Trauma	0	30 (29.7%)	30 (23.8%)
Retained Tissue	2 (8%)	3 (3%)	5 (4%)
IV Fluid Infusion	25 (100%)	98 (97%)	123 (97.6%)
Blood Transfusion	3 (12%)	1 (1%)	4 (3.2%)
Given Uterotonic for PPH Management	25 (100%)	92 (91%)	117 (92.9%)
Given Tranexamic Acid	22 (88%)	80 (79.2%)	102 (81%)
Referred	5 (20%)	16 (15.8%)	21 (16.7%)

FRU: First referral unit, HSC: Heat-stable carbetocin, IV: Intravenous, PPH: Post Partum Hemorrhage, N: Number of cases wherein HSC was used.

Table 3: Association between heat-stable carbetocin (HSC) use for postpartum hemorrhage (PPH) prevention and level of facility.

Indicator	FRU	non-FRU	Total	P Value
1. Cases received HSC for PPH prevention				
HSC use	11,289 (63.20%)	6572 (36.80%)	17,861	P < 0.001
HSC not Used	247 (38.84%)	389 (61.16%)	636	
Total	11,536 (62.37%)	6961 (37.63%)	**18,497**	
2. Cases received HSC within one minute of delivery				
HSC administered within one min	11,283 (63.93%)	6365 (36.07%)	17,648	P < 0.001
HSC administered after one min	6 (2.82%)	207 (97.18%)	213	
Total	11,289 (63.20%)	6572 (36.80%)	**17,861**	

FRU: First referral unit

during the implementation of the HSC model. Based on implementation learnings, the district authorities decided to scale-up the model in all 32 delivery points of Dewas district. Presently, discussions are ongoing for incorporation of the HSC model into the state program implementation plans, paving the way for a statewide scale-up.

DISCUSSION

Steps toward reducing the incidence and impact of PPH would significantly contribute to reducing maternal mortality and morbidity. Likewise, improving the overall quality of maternal healthcare to prevent and treat complications such as PPH is critical to attaining the Sustainable Development Goals Target 3.1.[15] Despite efforts to identify patients with increased risk for PPH, this life-threatening complication often occurs in women with no identifiable risk factors,[16] highlighting the importance of an effective uterotonic to be used in the third stage of labor. This study implemented an HSC model as part of the AMTSL strengthening initiative and reported no mortality amongst 18,497 cases managed and zero adverse events.

Guidelines are needed to provide optimal, evidence-based care to women experiencing PPH, especially if a newer drug is introduced into the health system. Capacity-building and supportive supervision led to a nearly universal use of uterotonics within one minute, proving an entry point for quality improvement of AMTSL practices. Even though there was an increase from 0.3% to 0.7% of reported PPH incidence, it could be because of better monitoring and the fact that all risk factors for PPH were not recorded in this study.

HSC must be used appropriately and not for labor induction or augmentation because even if the drug administration is discontinued immediately upon signs of fetal or maternal distress, the drug will remain active in the mother's body for a prolonged period, raising the risk of maternal and fetal death. This implementation model demonstrated that it is possible to ensure the appropriate use of HSC in public health delivery sites in India as per global recommendations. The data shows that the current public health drug management system can ensure uninterrupted availability, and in only <3.5% of cases was the HSC not used for PPH prevention with minimal or no wastage.

While HSC can only be used immediately after birth for PPH prevention, oxytocin is still required for labor, delivery, and postpartum, as it has multiple uses. This necessitates vital drug procurement planning and will need information from large-scale multicentric studies to estimate the correct quantity of quality-assured drugs that need to be procured. The results showed that 2.9% of the admissions were deliveries occurring outside the facility, mainly in transit (88%), highlighting the importance of birth preparedness as an essential intervention for scale-up in countries.

Our study highlights a notable disparity in the utilization of HSC for preventing PPH between non-FRU-level facilities

and FRU facilities. This difference may be attributed to insufficient knowledge and skill acquisition among non-FRU staff concerning the indications and contraindications of this newer drug, despite receiving a day-long training on HSC use prior to implementation of intervention. Given that HSC is a newer drug for the public health settings, the fear, and concerns among non-FRU staff regarding its potential misuse in contraindicated cases could possibly be a reason for its relatively lower uptake. Other factors such as the unavailability of specialist doctors and lack of adequate infrastructure and equipment to manage PPH-related complications at non-FRU-level facilities may also contribute to the lower adoption of HSC use. Similar obstacles have been identified as key barriers in previous studies on the uptake of misoprostol for PPH prevention in LMICs.[17]

Additionally, our study revealed higher compliance with HSC use recommendations, particularly the administration of HSC within one minute of delivery, in FRU facilities compared to non-FRU facilities. This underscores the need for establishing a structured mechanism for supportive supervision for health staff posted at non-FRU facilities to increase and ensure its optimal use.[18]

Delays in detecting or treating PPH can result in complications or death. A blood collection drape can help provide an objective, accurate, and early diagnosis of PPH, and delayed or inconsistent use of effective interventions could be addressed by a treatment bundle. The E-MOTIVE intervention resulted in a 60% lower risk of the primary outcome—a composite of severe PPH, laparotomy for PPH, or maternal death from PPH.[19] In this study, PPH was diagnosed by health providers based on visual estimations and may be a factor in the under-reporting of PPH, but no death was reported. A recent Cochrane review showed no evidence that quantitative estimation of blood loss reduces the need for uterotonic agents, blood transfusion, or volume expanders during PPH.[20]

The findings of our study confirm the appropriate use of HSC and its implementation feasibility in controlled public health settings. However, initial procurement of a newer uterotonic like HSC, maintaining its optimal as well as ensuring its uninterrupted supply, could be challenging while going to scale country-wide or while planning replication of this initially implemented model in similar settings of other LMICs.

While the cost-effectiveness of HSC has been well established, the principal hurdle lies in the initial higher procurement costs within the public health system. This requires high-level advocacy to convince the key decision-makers to procure HSC using their existing financial resources.

Carbetocin, an oxytocin analog, has been used for the prevention of PPH since 1997. The molecular differences enhance the stability of carbetocin, making it possible to formulate carbetocin into a highly stable product. Despite this, there is a potential risk of the public health system procuring nonstable variants, emphasizing the necessity for structured training on HSC targeting senior leadership and key decision-makers at both state and national levels. These trainings will be crucial to ensure that the procurement of HSC is reliable, effective, and adheres to stringent quality standards.

Strengths and Limitations of the Study

The main strength is that to the best of our knowledge, this is the first study from India on the use of HSC, which determined the feasibility and assessed the optimal use of HSC in the existing public health system. The results of this study can be used for policy decision-making and program purposes for using HSC as an alternative to oxytocin for the prevention of PPH in settings where oxytocin is of suspect quality.

Limitations of our study include data analysis on deliveries carried out at intervention facilities captured during the study time frame. We did not include women who gave birth while in transit (i.e., on their way) in the analysis due to insufficient documentation regarding the administration of uterotonics in such deliveries. Additionally, we did not collect additional data to ascertain the underlying reasons for relatively lower HSC utilization in non-FRU facilities. The potential factors might involve a higher incidence of contraindicated cases in non-FRU settings or issues related to knowledge, skills, fear, and apprehension among staff regarding the use of this newer drug for PPH prevention. Further research is necessary to delve into these reasons; however, such an investigation was beyond the scope of the current study.

CONCLUSION AND GLOBAL HEALTH IMPLICATIONS

The PPH continues to pose a significant clinical risk for maternal morbidity and mortality. There is a need for implementing global evidence-based recommendations, including using new uterotonics such as HSC, where the quality of oxytocin remains suspect. The results of our study suggest safe and appropriate utilization of HSC in line with the WHO recommendations within India's public health system, making it a critical starting point for reinforcing AMTSL practices. The initial outcomes of implementing the HSC model in controlled settings are feasible for introduction and appropriate to use. It is crucial to comprehend how the

existing supply chain and healthcare system adapt to and ensure the optimal utilization of HSC at the most remote levels while scaling up this model to other geographies.

Key Messages

- Our study demonstrated the feasibility of introducing Heat-Stable Carbetocin (HSC) and its appropriate use for postpartum hemorrhage (PPH) prevention in the existing health system of Madhya Pradesh, India.
- HSC is an alternative to oxytocin for preventing PPH in settings where oxytocin quality cannot be guaranteed. Capacity building of healthcare providers during Active Management of the Third Stage of Labor (AMTSL) will increase the effectiveness of care.
- Health system adaptations are necessary to ensure the optimization of HSC utilization and sustainable scale-up.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest

All the authors declare no conflict of interest. USAID provided financial assistance for implementation through IPE Global as an implementation partner.

Financial Disclosure

Nothing to declare.

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Ethics Approval

This study was approved by Institutional Review Board (IRB) of the International Institute of Health Management Research (IIHMR), New Delhi. The approval number is IIHMR/D/SRB/2 and date is 20 July 2022.

Declaration of Patient Consent

Patient's consent is not required as patient's identity is not disclosed or compromised.

Use of Artificial Intelligence (AI)-Assisted Technology for Manuscript Preparation

The authors confirm that there was no use of AI-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Special Collection

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RESEARCH

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Cost-effectiveness and budget impact of heat-stable carbetocin compared to oxytocin and misoprostol for the prevention of postpartum hemorrhage (PPH) in women giving birth in India

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Abstract

Introduction Low- and middle-income countries (LMICs) are committed to achieving the Sustainable Development Goal 3.1 to reduce maternal mortality. The Ministry of Health and Family Welfare of India recommends prophylactic uterotonic administration to every woman following delivery to reduce the risk of postpartum hemorrhage (PPH), as PPH is the leading cause of maternal mortality in LMICs, including India. In 2018, the World Health Organization first recognized heat-stable carbetocin for PPH prevention. Governments are now considering its introduction into their public health systems.

Methods A decision-tree model was developed from the public healthcare system perspective to compare the value of heat-stable carbetocin versus oxytocin and misoprostol among women giving birth in public sector healthcare facilities in India. The model accounted for differences in PPH risk and costs based on mode of delivery and healthcare setting, as well as provider behavior to mitigate quality concerns of oxytocin. Model outcomes for each prophylactic uterotonic included the number of PPH events, DALYs due to PPH, deaths due to PPH, and direct medical care costs. The budget impact was estimated based on projected uterotonic uptake between 2022–2026.

Results Compared to oxytocin, heat-stable carbetocin avoided 5,468 additional PPH events, 5 deaths, and 244 DALYs per 100,000 births. Projected direct medical costs to the public healthcare system were lowered by US $171,700 (₹12.8 million; exchange rate of ₹74.65 = US$1 from 2 Feb 2022) per 100,000 births. Benefits were even greater when compared to misoprostol (7,032 fewer PPH events, 10 fewer deaths, 470 fewer DALYs, and $230,248 saved per 100,000 births). In the budget impact analysis, India's public health system is projected to save US$11.4 million (₹849 million) over the next five years if the market share for heat-stable carbetocin grows to 19% of prophylactic uterotonics administered.

Conclusions Heat-stable carbetocin is expected to reduce the number of PPH events and deaths, avoid more DALYs, and reduce costs to the public healthcare system of India. Greater adoption of heat-stable carbetocin for the prevention of PPH could advance India's efforts to achieve its maternal health goals and increase efficiency of its public health spending.

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Keywords Postpartum hemorrhage, Uterotonics, Cost-effectiveness, Budget impact, Economic analysis, Health economic modeling

Introduction

Universal health coverage and maternal health

In 2015, nations worldwide committed to achieve both the 2030 Agenda for Sustainable Development (SDG) and Universal Health Coverage (UHC), representing a promise of quality health services while limiting financial burden [1]. These were bold commitments for low- and middle-income countries (LMICs), where increasing burden of disease and expanding populations are rapidly growing demand for health services, while health budgets remain underfunded [2]. Perhaps there is no greater example of country commitment to SDG and UHC than in maternal health as stated in SDG 3.1 – to reduce the Maternal Mortality Ratio (MMR) to less than 70 per 100,000 births [3]. Despite these commitments, without strengthened interventions, particularly in poorer states, reaching the country's SDG 3.1 will remain difficult to achieve [3]. This challenge is seen in India, where despite impressive reductions in India's MMR from 370 per 100,000 live births in 2000 to 113 in 2018, equitable access to quality maternal care remains elusive for many women during their pregnancy journey [4, 5].

Postpartum hemorrhage and prophylactic uterotonics

Although largely preventable, postpartum hemorrhage (PPH) is the leading cause of maternal mortality, particularly in LMICs [6], with uterine atony the most frequent cause of PPH [7]. Globally, PPH affects 14 million mothers annually, and almost half a million mothers died of PPH between 2003—2009 [8]. A recent global randomized clinical trial in PPH prevention found that 9% of women who gave birth vaginally experienced PPH [9], imposing significant burden in LMICs. In India, for example, PPH accounts for 26.1% of maternal deaths [8].

The use of an effective uterotonic is universally recognized as the most important medical intervention to prevent PPH. When compared with physiological management, prophylactic drugs reduce the risk of PPH by 66% [10]. Based on this evidence, the World Health Organization (WHO) recommends use of an effective uterotonic to prevent PPH during the third stage of labor for all births [11]. In 2018, a Cochrane Review was conducted to identify the most effective uterotonic agent(s) to prevent PPH with the most limited adverse events [12]. Although oxytocin is the most widely used agent globally, the network meta-analysis (U-NMA) showed that other therapies – oxytocin plus misoprostol and oxytocin/ergometrine combinations and carbetocin (stand-alone) – are associated with higher efficacy. However, the two combination regimens were associated with increased side effects, whereas carbetocin had no increase in side effects as compared with oxytocin. As for misoprostol alone, the U-NMA suggests that it is both less effective in preventing PPH compared to the above alternatives, including oxytocin, and has undesirable side-effects [12]. Despite this new network meta-analysis, oxytocin and misoprostol remain the two most widely used uterotonics to prevent PPH.

In practice, the quality of these two most widely administered uterotonics in LMICs may be poor due to manufacturing or degradation during transport and storage or exposure to climactic conditions, thereby compromising their effectiveness in preventing PPH. Because oxytocin requires constant refrigeration [13], suboptimal storage conditions in LMICs have led to widespread reports of deterioration of the quality [14–16]. The quality of misoprostol is also adversely impacted by high humidity in LMICs and poor packaging. In 2020, a systematic review across 40 LMICs further confirmed that oxytocin and misoprostol are often of poor quality with nearly 40% of each failing quality tests [17].

The updated 2018 WHO recommendations recognized alternative uterotonics when oxytocin quality was circumspect [11]. Among the alternatives, heat-stable carbetocin was included for the first time based on its efficacy, safety, and heat-stability characteristics. With a shelf-life of 48 months at 30 °C, the heat-stable formulation of carbetocin can withstand extended exposure to higher temperatures [18]. Unlike oxytocin [19] and misoprostol [12, 19], heat-stable carbetocin does not require refrigeration nor is it susceptible to humidity, and therefore seems an appropriate alternative for use, to mitigate aforementioned concerns, particularly in LMICs [13].

Health technology assessment

Access to an effective and high-quality uterotonic to prevent PPH is a key component to achieving maternal health and UHC goals. Country prioritization of maternal health typically takes form through programs that provide free or subsidized access to maternal services, including medicines. Because LMIC governments are generally fully responsible for procurement and provision of these commodities, LMIC governments, such as India, are increasingly demanding

health technology assessments (HTAs) – including cost-effectiveness and budget impact analyses – to assist programmatic and procurement decision-makers in evidence-based priority-setting of interventions [20, 21]. Health Technology Assessment in India (HTAIn) is one example of growing LMIC demand for evidence-based healthcare decision-making [22]. HTAs can also help challenge programming and purchasing behaviors that prioritize the up-front price of an intervention by showcasing the holistic efficiency and implications of current versus alternative interventions. For these reasons, HTA can be an invaluable tool to support SDG and UHC achievement.

As India and other LMICs seek to further address PPH as part of their SDG 3.1 and UHC commitments, assessing the updated WHO recommendation on uterotonics for the prevention of PPH as part of a formal HTA is, perhaps, warranted in support of prioritization-based decision-making. To this end, a health-economic model was developed to assess the cost-effectiveness and budget impact of prophylactic uterotonics. In this paper, the model is used to assess the potential role of heat-stable carbetocin as a new prophylactic uterotonic in India – at its public sector, subsidized price – compared to oxytocin and misoprostol, the two most widely used uterotonics for the prevention of PPH [23].

Methods

Cost-effectiveness model structure

A decision tree model was developed based on the choice of uterotonic for the prevention of PPH, aligned with the WHO 2018 recommendations, to evaluate the cost-effectiveness of heat-stable carbetocin to prevent PPH compared to oxytocin and misoprostol, the two most widely used prophylactic uterotonics, from India's public healthcare system perspective. Figure 1 shows the possible paths for women through the decision tree. Women receive a prophylactic uterotonic immediately after vaginal or caesarean section delivery (C-section), with some women requiring retreatment with additional uterotonics to treat uterine atony. Despite the use of a prophylactic uterotonic, some women may experience a PPH event that is classified as either mild/moderate PPH (500–1000 mL blood loss) or severe PPH ($\geq$1000 mL blood loss). The risk of suffering either a mild/moderate or severe PPH differs by method of delivery, with C-section delivery of higher risk. Women with severe PPH are at greatest risk of death and often require transfer to a higher-level health care facility. Because the risk of PPH, death due to PPH, and costs differ by healthcare setting (primary, secondary, or tertiary facility), the decision tree is replicated for each setting in the model. Results from each tree are then weighted based on the proportion of deliveries occurring in each healthcare setting to obtain the overall results for the prophylactic uterotonic.

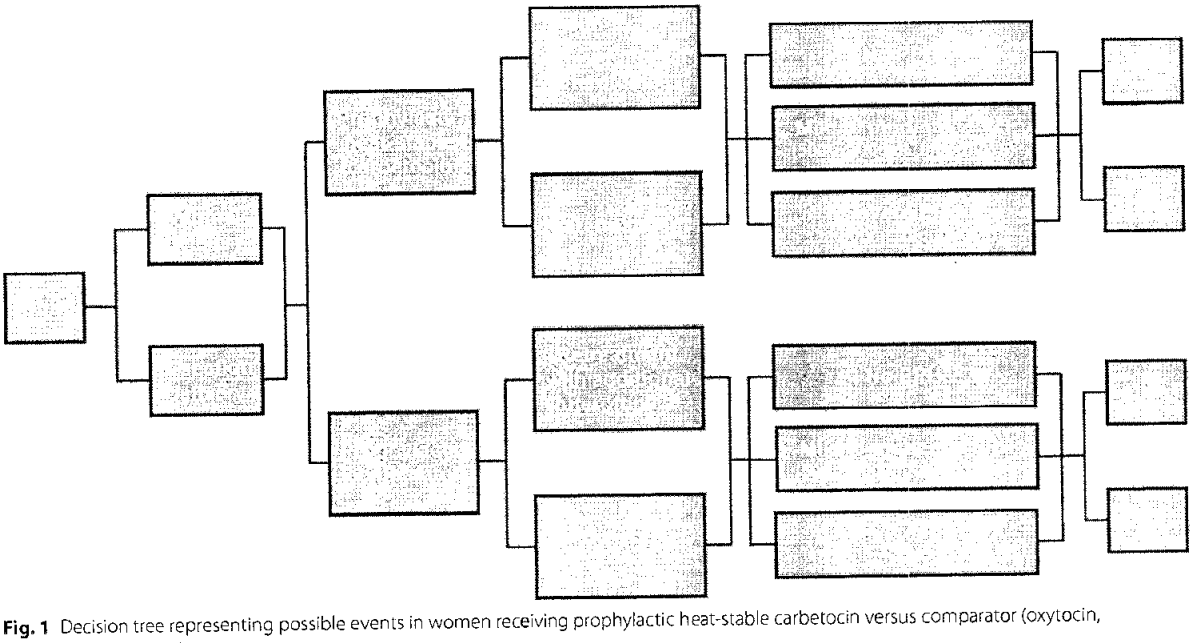

Fig. 1 Decision tree representing possible events in women receiving prophylactic heat-stable carbetocin versus comparator (oxytocin, misoprostol) per healthcare setting

Model inputs

Inputs for the model were sought from published literature, with local data utilized when available. When no referenceable source was identified, inputs were based on expert opinion from Indian clinical experts.

Population and delivery characteristics

We considered a cohort of 100,000 women giving birth in India across primary (PHC; includes both primary health centers and community health centers), secondary (SHC; includes District and sub-District hospitals) or tertiary (THC; includes Regional/Central-level institutions and Super specialty hospitals) public healthcare facilities, with characteristics provided in Table 1. Of these deliveries, 14.3% are performed via C-section [24], with the remaining 85.7% vaginal deliveries. The age distribution of women giving birth at a healthcare center was taken from the Indian state of Karnataka, assumed to be representative of the broader Indian population [25]. The percentage of pregnant women with anemia (hemoglobin $\leq$ 110 g/L) was obtained from key opinion leaders. Estimates differed by healthcare setting, with the highest (70%) and lowest (30%) percentage with anemia found in primary and tertiary healthcare centers, respectively. These estimates were consistent with an overall estimate of 50% based on data from The World Bank Group [26] and with the 2019–2021 Indian National Family Health Survey—5. The percentage of women in India with severe anemia (hemoglobin $\leq$ 90 g/L) was derived by healthcare setting based on an estimate that 9.4% of women with anemia experience severe anemia [27].

Efficacy of Prophylactic Uterotonics

The efficacy of prophylactic uterotonics was based on results from a 2018 Cochrane Review of uterotonic agents for preventing postpartum hemorrhage: a network meta-analysis (U-NMA) [12]. Data were taken from 135,559 women in the third stage of labor from 196 trials across 53 high-, middle- and low-income countries. Women undergoing both vaginal and caesarean births were included. Most trials were carried out in hospital settings with women undergoing vaginal births. Primary outcomes were the relative effects and rankings of each uterotonic for prevention of mild/moderate PPH and of severe PPH.

Based on a study by Nyfløt et al., pregnant women with severe anemia (hemoglobin $\leq$ 90 g/L) are at elevated risk of severe PPH, with an odds ratio of 4.27 (95% confidence interval: 2.79, 6.54) [27]. Because the risk of severe anemia in India differs by type of healthcare facility, an adjustment was made to the efficacy estimates from the U-NMA to account for this difference. We first estimated the risk of PPH with and without severe anemia based on the estimated percentage of women in the U-NMA with severe anemia (2.82%, or 9.4% of the 30% with anemia are severe). Next, these estimates were weighted based on the percentage of women with and without severe anemia by healthcare center in India (from Table 1). Because the risk of severe anemia is the same for the U-NMA and tertiary healthcare centers in India (2.82%), the PPH risks in a tertiary healthcare center are taken directly from the U-NMA, while the risks in a primary and secondary healthcare center are higher due to the higher

Table 1 Model inputs for delivery and women characteristics

Input Parameter		Estimate (%)	Source
Healthcare Setting	Primary	44%	Guttmacher Institute (2016) [28]
	Secondary	32%	
	Tertiary	24%	
Type of Delivery	C-section	14.3%	IIPS (2021) [24]
	Vaginal	85.7%	
Age of women (years)	15–19	2.2%	eJanMa (2015) [25]
	20–24	54.8%	
	25–29	31.6%	
	30–34	8.8%	
	35–39	2.1%	
	40–44	0.4%	
	45 and above	0.1%	
Women with anemia (Hgb $\leq$ 110 g/L) by healthcare center	Primary	70%	Indian clinical experts
	Secondary	50%	
	Tertiary	30%	
Women with severe anemia (Hgb $\leq$ 90 g/L) by healthcare center	Primary	6.6%	Nyfløt et al. (2017) [27]
	Secondary	4.7%	
	Tertiary	2.8%	

percentage of women with severe anemia in these settings (see Table 2). Data from the U-NMA was also used for the proportion of women requiring re-treatment and the proportion of women requiring blood transfusions is also shown in Table 2.

Healthcare resource use and costs

The model captured direct costs to the healthcare system, which included drug costs for acquisition of the drug itself (initial prophylactic and additional uterotonics for PPH treatment), administration and cold-chain costs, as well as costs for healthcare providers, blood transfusions, hospitalizations, and referrals. The acquisition cost of US$0.38 (₹28.34; exchange rate of ₹74.65 = US$1 from 2 Feb 2022 [29]) for heat-stable carbetocin was based on a single-time administration through an IM/IV injection dose of 100 μg [23]. For oxytocin, while the Ministry of Health and Family Welfare (MoHFW) recommends 10 IU, the model used an average prophylactic dose administered of 17.28 IU (to account for local provider behavior that regularly seeks to mitigate quality concerns by increasing the dose) [30] at an acquisition cost of $0.24 (₹17.78) per 10 IU (Karnataka Antibiotics Pvt Ltd). For misoprostol, following MoHFW guidance, a prophylactic dose of 600 μg, priced at an acquisition cost of $0.015 (₹1.12) per 200 μg tablet, was applied. For those requiring additional uterotonics to treat PPH, the Indian clinical experts assumed 75% of women would receive oxytocin alone (40 IU) and 25% of women would receive oxytocin (40 IU) with misoprostol (800 μg) regardless of healthcare center type. All acquisition costs included 12% GST and 14% for channel partner and distribution.

Drug administration and logistics costs are also included. Administration costs for heat-stable carbetocin and oxytocin included the cost of syringe ($0.035) and 5 min of nurse/midwife time (at an average monthly salary of $380); for misoprostol, 2 min of nurse/midwife time as estimated per local experts. Cold-chain costs for logistics ($0.076) and storage ($0.049) per ampoule, and wastage (32%) were included related to oxytocin [31, 32].

Healthcare resource utilization costs associated with personnel, hospital stay, blood transfusion, referrals and follow-up care were captured for each birth by healthcare center type based on Indian clinical expert insights and inflated to 2021 costs (see Supplementary materials 1, Table S1 for additional cost input details).

Risk of mortality

PPH impact on mortality is also captured in the model. However, estimates for the risk of mortality due to PPH are not directly available for India. Instead, the MMR and the percentage of deaths due to PPH were used to obtain the expected number of deaths due to PPH per 100,000 women. This number was then divided by the estimated number of PPH events per 100,000 women, which is determined based on the efficacy for each prophylactic uterotonic and their respective market share from the first year in the budget impact model. For India, the MMR is 113 (2018 estimate) [4], with 26.1% of the deaths due to PPH (estimate for Southern Asia) [8]. Based on an assumed current market share of 80% oxytocin and 20% misoprostol, the resulting overall risk of mortality due to PPH is 0.16%.

Table 2 Risk of PPH[a], use of additional uterotonics and blood transfusions (based on Cochrane Review U-NMA)

Intervention	Risk of PPH[a]						Additional uterotonics	Blood transfusions
	Primary Healthcare Center[b]		Secondary Healthcare Center		Tertiary Healthcare Center			
	Mild / moderate PPH	Severe PPH	Mild / moderate PPH	Severe PPH	Mild / moderate PPH	Severe PPH		
Vaginal delivery								
Heat-stable carbetocin	6.40%	2.87%	6.25%	2.73%	6.1%	2.6%	5.2%	1.2%
Oxytocin	9.60%	3.30%	9.40%	3.15%	9.2%	3.0%	11.6%	1.5%
Misoprostol	10.00%	3.96%	9.80%	3.78%	9.6%	3.6%	12.1%	1.3%
C-section delivery								
Heat-stable carbetocin	32.19%	12.48%	32.04%	12.04%	31.9%	11.6%	13.7%	6.6%
Oxytocin	47.13%	14.26%	47.12%	13.78%	47.1%	13.3%	30.4%	8.1%
Misoprostol	49.27%	16.85%	49.33%	16.33%	49.4%	15.8%	31.6%	7.1%

[a] Risk of PPH is adjusted for percentage with severe anemia by healthcare center type (PHC: 6.6%, SHC: 4.7%, THC: 2.8%)

[b] It is recognized that few PHC facilities in India conduct C-section deliveries (likely in only some community health centers). The model is showing the risk of PPH based on additional risk factors at PHC level, including the risk of not being transferred when indicated

The model required risk of death due to PPH stratified by severity of PPH and type of healthcare center. These were obtained through calibration (to obtain the overall risk of 0.16%) by using the odds ratios for mortality for several factors (maternal age, type of healthcare facility, actual referrals to another facility and risk of death due to referral and severity of PPH). Insights from Indian clinical experts were used to obtain the likelihood of mortality associated with severe PPH events relative to mild/moderate PPH events (estimate of 3.46). The odds ratio for mortality during referral to another hospital is estimated to be 13.35 [33]. According to local experts, it is assumed that all women experiencing a severe PPH event while in a PHC or SHC facility should be referred to a SHC or THC facility, respectively, with 45% of them actually transferred. Odds ratios for the risk of mortality were obtained from Tort et al. (2015) for healthcare setting (2.43 for PHC; 1.49 for SHC; 1.00 for THC) and maternal age (1.00 for ages less than 20; 1.48 for ages between 20 and 35; 2.16 for ages above 35) [33]. The resulting estimates for the risk of mortality due to PPH stratified by healthcare setting and severity of PPH used in the model are shown in Table 3.

Disability-adjusted life years

Disability-adjusted life years (DALYs), the preferred health outcome by WHO for presenting results of cost-effectiveness [34], were estimated for each prophylactic treatment based on the number of non-fatal and fatal PPH events. For non-fatal PPH events, DALYs were estimated based on the magnitude of the disability and its duration. The duration of disability due to mild/moderate PPH (30 days) and severe PPH (90 days) were obtained from Lubinga et al. (2015) [35], Seligman et al. (2006)[36] and Indian clinical experts. Disability weights for mild/moderate (0.166), and severe PPH (0.473 for days 0–30, 0.324 for days 31–90) were taken from the Global Burden of Disease study [37].

DALYs were also accumulated from life years lost due to premature death following a fatal PPH events. For each death, remaining life years lost was estimated using life table information for females in India [38] and the maternal age at delivery. Because DALYs due to fatal-PPH events accumulate in the future, life years lost were discounted 3% per year.

Table 3 Risk of mortality following PPH event by severity and healthcare setting

PPH Severity	Healthcare Setting		
	PHC	SHC	THC
Mild/Moderate	0.04%	0.02%	0.01%
Severe	0.80%	0.49%	0.05%

Model output

Cost-effectiveness

To support assessment and decision-making related to heat-stable carbetocin as a new alternative for the prevention of PPH versus current uterotonics, the incremental cost, number of PPH events avoided, number of deaths due to PPH avoided and DALYs averted are obtained for heat-stable carbetocin versus oxytocin alone and misoprostol alone. The incremental cost-effectiveness ratio (ICER), as measured by the incremental cost per DALY averted, was calculated for heat-stable carbetocin vs each of the alternative prophylactic uterotonics. (Note: the ICER is not reported if heat-stable carbetocin decreases both the costs and DALYs against the comparator uterotonics, as there is no incremental cost to avert a DALY.) To declare an intervention to be cost-effective, we used a willingness-to-pay threshold equivalent to the 2020 per capita GDP in India of $1,900.75 (₹141,891), as per India's HTAIn policy.

Robustness of the results to uncertainty in model parameters were evaluated in both one-way sensitivity analyses (OWSA, to isolate the impact of one parameter using extreme values) and probabilistic sensitivity analyses (PSA, to assess the joint impact of uncertainty in multiple parameters across the range of likely values). (See Supplementary materials 1, Table S2 for input values and distributions). Results for the PSA were based on 5,000 random sets of the parameters drawn from their statistical distribution.

Finally, scenario analyses were performed to determine the impact alternative model settings and choice of input sources have on the cost-effectiveness of heat-stable carbetocin vs oxytocin and misoprostol. The scenarios were selected based on maternal health and supply chain stakeholder interests. Four scenarios associated with cold-chain costs were evaluated, including where cost-chain costs were excluded based on the assumption that cold-chain will be required for other medicines regardless if heat-stable carbetocin is used prophylactically or not [31, 32]. Two separate scenarios, where a lower oxytocin dose (to the recommended level of 10 IU) and lower misoprostol dose (400 μg), were considered, aligning with WHO recommendations; in both scenarios, no reduction in efficacy was assumed. A scenario where the base-case acquisition costs for oxytocin and misoprostol were both reduced by 25% was analyzed to consider price sensitivity differences. A scenario reflecting the impact of using efficacy estimates for oxytocin and heat-stable carbetocin using data from CHAMPION was assessed, the largest clinical trial in PPH prevention [39]. Finally, scenarios were evaluated with alternative sources for the percentage of women with anemia [24, 26], age distribution of

women giving birth [36] and the duration of hospitalization (Indian clinical experts) to support further country contextualization.

Budget impact analysis

A budget impact analysis was also conducted by projecting the annual cost to the healthcare system for births at public institutions based on the current estimated market share of uterotonics ("current environment") and based on a potential shift in market share with uptake of heat-stable carbetocin ("new environment") over the next 5 years per discussion with local experts in India (see Table 4). The budget depends on the total number of births from 2022 through 2026, which was estimated using a crude rate of 18.083 births per 1,000 persons in a population of 1,352,617,328 in 2018 with an annual growth rate of 1.04% [26]. Of these births, 88.6% are institutional births, of which 61.9% occur in a public facility [24]. The distribution of births by healthcare facility type and type of delivery, along with clinical and healthcare resource use inputs are the same as used in the cost-effectiveness analysis.

Results

Cost-effectiveness analysis

In the comparison versus oxytocin, administering heat-stable carbetocin for PPH prevention resulted in fewer PPH events (28.0% reduction overall), deaths and DALYs. In the comparison versus misoprostol, administering heat-stable carbetocin for PPH prevention resulted in an even greater reduction in PPH events (33.3% reduction overall), deaths and DALYs. (See Table 5 for results for the three prophylactic uterotonics).

Total costs to the public healthcare system are lowest when heat-stable carbetocin is selected as the prophylactic uterotonic administered (see Table 5). These cost benefits can largely be attributed to the greater efficacy of heat-stable carbetocin in preventing more PPH events. A breakdown of costs by category are provided in Supplementary materials 2 (see Table S3) and reveals savings with heat-stable carbetocin across all cost categories except follow-up costs (which are assumed to be the same) compared to oxytocin and across hospital-related costs (hospital stay, personnel, blood transfusions and referrals) compared to misoprostol.

From a cost-effectiveness standpoint – combining health outcomes and healthcare costs – heat-stable carbetocin out-performs both oxytocin and misoprostol from the public healthcare system perspective in India, as it lowers costs and DALYs are averted. This result is observed across each of the three healthcare facility types (see Supplementary materials 2, Table S4). In the comparison versus oxytocin, health outcomes for heat-stable carbetocin are improved the most for births in the PHC (e.g., 0.003 DALYs averted per woman), while the cost reduction is the greatest in the THC ($2.42 decrease per birth).

Sensitivity analyses

The OWSA were conducted comparing oxytocin vs each of the prophylactic uterotonics separately for the incremental DALYs and incremental costs. The resulting tornado diagrams show the 10 most influential parameters for both measures (see Supplementary materials 3, Figures S1 and S2). Across all comparisons, the parameters with the greatest impact on DALYs averted are predominantly related to mortality, referrals, and the proportion of C-section deliveries, whereas those with the greatest impact on the incremental cost are related to the duration of hospital stay. Regardless of the parameter varied, costs are always lower and DALYs are averted with heat-stable carbetocin compared to oxytocin and misoprostol.

Results of the PSA are displayed in Fig. 2 with the PSA replicates of the incremental costs and DALYs avoided

Table 4 Market share of prophylactic uterotonics under current and new environment (2022–2026)

Intervention	2022	2023	2024	2025	2026
Current Environment (without Heat-Stable Carbetocin)					
Oxytocin	80%	80%	80%	80%	80%
Misoprostol	20%	20%	20%	20%	20%
New Environment (with Heat-Stable Carbetocin)					
Heat-stable carbetocin	0.2%	2%	6%	13%	19%
Oxytocin	79.8%	78%	75%	69%	63%
Misoprostol	20%	20%	19%	18%	18%

Table 5 Total PPH events, deaths, DALYs and Costs per 100,000 births

Intervention	Total PPH events	Severe PPH events	Deaths	DALYs	Total cost (in $)	Total cost (in ₹)
Heat-stable Carbetocin	14,070	4,100	25	1,170	13,990,033	1,044,355,971
Oxytocin	19,538	4,711	30	1,414	14,161,733	1,057,173,404
Misoprostol	21,102	5,618	35	1,640	14,220,281	1,061,543,962

for heat-stable carbetocin versus each prophylactic uterotonic. Heat-stable carbetocin out-performs both oxytocin (Fig. 2A) and misoprostol (Fig. 2B); nearly all (98.0% and 98.9%, respectively) of the PSA replicates indicate heat-stable carbetocin lowers costs and averts more DALYs than either alternative prophylactic uterotonic.

Scenario analysis

Across the scenario analyses, heat-stable carbetocin continued to out-perform both oxytocin and misoprostol (see Supplementary materials 3, Table S5). Heat-stable carbetocin, as a prophylactic alternative, continued to produce the lowest costs compared to oxytocin and misoprostol, despite scenario changes:

- excluding cold-chain costs for oxytocin lowered the savings versus oxytocin from $1.72 to $1.50 per birth and versus misoprostol from $2.30 to $2.29 per birth.
- use of an alternative source for cost-chain costs resulted in savings per woman ranging from $1.67 to $2.49 per birth and $2.30 to $2.36 per birth compared

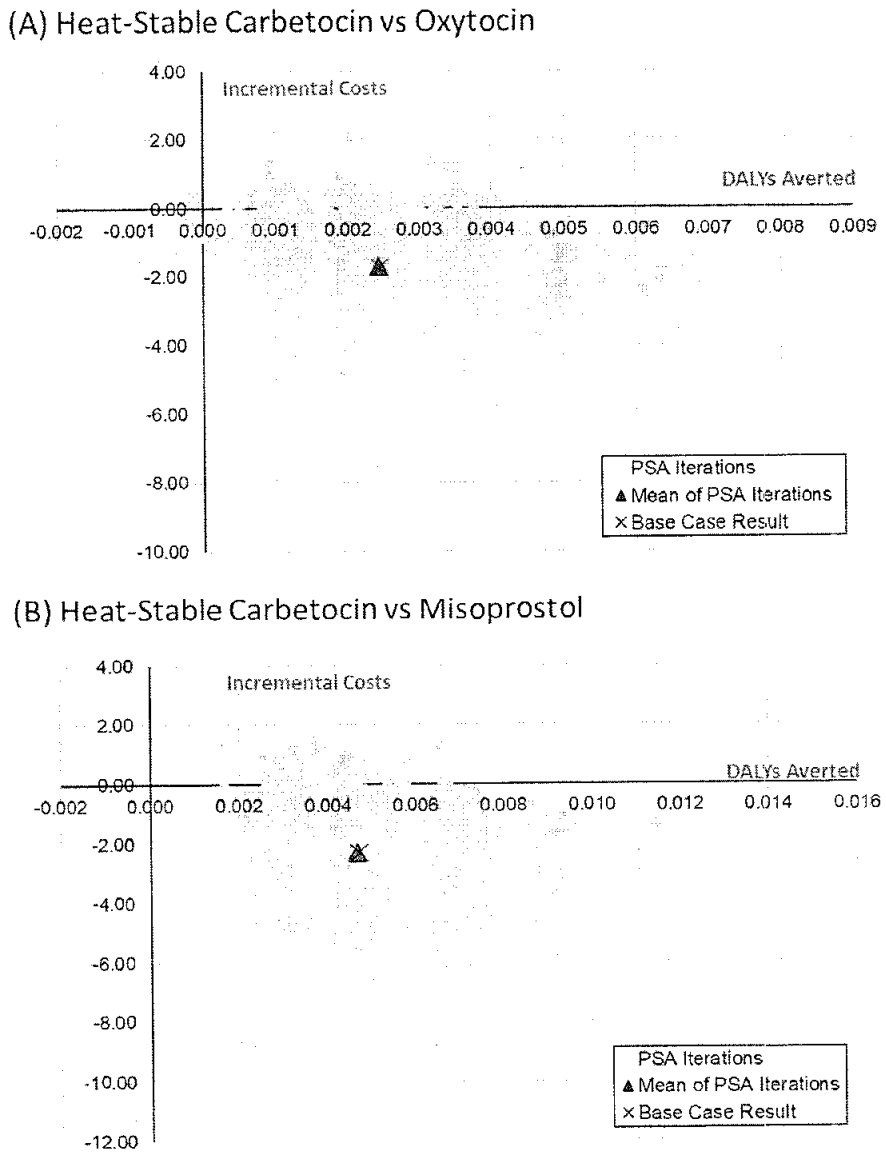

Fig. 2 Probabilistic sensitivity analysis results for incremental costs and DALYs averted. **A** Heat-stable carbetocin versus oxytocin and (**B**) Heat-stable carbetocin versus misoprostol

to oxytocin and misoprostol, respectively, depending on the source of costs.
- setting the average dose for prophylactic oxytocin to 10 IU (recommended dose by the MoHFW of India) lowered the savings ($1.54 per birth).
- reducing oxytocin and misoprostol pricing by 25% lowered the savings to $1.57 and $2.27 per birth compared to oxytocin and misoprostol, respectively.
- replacing the source for efficacy with the CHAMPION trial resulted in savings of $0.82 per birth compared to oxytocin.

Budget impact analysis

From 2022 through 2026, 71.4 million cumulative births were projected in public healthcare facilities in India (see Table 6) [24]. During this period, costs to the public healthcare system are projected to decrease by $11.4 million (₹849.2 million), based on incremental growth in heat-stable carbetocin integration – reaching 19% of prophylactic uterotonic use by 2026 – compared to projected costs based on current prophylactic oxytocin and misoprostol utilization patterns (without inclusion of heat-stable carbetocin). These budget savings are driven by approximately 322,000 fewer PPH events projected to occur.

Discussion

Our analysis focused on comparing a novel uterotonic – heat-stable carbetocin – to the most widely used uterotonics – oxytocin (standard of care) and misoprostol – for the prevention of PPH. We sought to assess the impact heat-stable carbetocin uptake may have on the Indian public healthcare system. Our findings show that the introduction of prophylactic heat-stable carbetocin is a cost-effective intervention driven by fewer total PPH events. These fewer PPH events – 28% to 33% fewer compared to prophylactic oxytocin and misoprostol, respectively – lead to improved overall health outcomes and, subsequently, cost savings to the Indian health system. Our findings indicate the public health system is projected to save $11.4 million (₹849 million; exchange rate of ₹74.65 = US$1 from 2 Feb 2022 [29]) over the next 5 years (2022 – 2026) if heat-stable carbetocin uptake reaches 19% of all births by 2026. Finally, our analysis suggests that if uptake of heat-stable carbetocin is more rapid, reaching, for example, 50% of all births by year 5, savings are projected to rise to $29.9 million (₹2.23 billion [36]).

Our results are consistent with recent analyses that signaled the ability of heat-stable carbetocin to prevent the greatest number of PPH events compared to oxytocin and misoprostol. Based on a model by Matthijsse et al. (2022) for the UK, carbetocin was associated with 3.42 fewer PPH events and 0.39 fewer severe PPH events per 100 women compared to oxytocin [40]. While overall rates for PPH were lower in the UK compared to India, both their model and ours suggest that roughly one out of every 9 avoided PPH events was severe. As with our model, they found carbetocin resulted in total cost savings. A similar result was found for Canada by Barrett, et al. (2022) where cost savings of carbetocin versus oxytocin were again primarily attributed to avoiding consequences of PPH [41]. In another cost-effectiveness evaluation for the UK, Pickering, et al. (2018) found carbetocin to lower the risk of total and severe PPH events, which in turn resulted in a lower total cost compared to misoprostol [42].

LMICs have committed to achieving SDG 3.1 by 2030. Although progress is being made, many countries are unlikely to meet this goal at their current pace [43]. PPH remains the leading direct cause of maternal mortality

Table 6 Projected annual budget and clinical impact of new versus current market share for uterotonics

	2022	2023	2024	2025	2026
Total Births	13,979,677	14,124,691	14,271,210	14,419,249	14,568,823
Total Costs ($)					
Current environment	1,975,973,855	1,996,471,093	2,017,180,954	2,038,105,644	2,059,247,390
New environment	1,975,920,321	1,995,930,198	2,015,491,503	2,034,415,603	2,053,845,363
Budget impact	-53,534	-540,895	-1,689,452	-3,690,041	-5,402,026
Total Costs (₹)					
Current environment	147,506,448,280	149,036,567,126	150,582,558,253	152,144,586,306	153,722,817,641
New environment	147,502,451,954	148,996,189,314	150,456,440,696	151,869,124,773	153,319,556,370
Budget impact	**-3,996,326**	**-40,377,812**	**-126,117,556**	**-275,461,533**	**-403,261,272**
Total PPH Events					
Current environment	2,633,715	2,661,035	2,688,639	2,716,529	2,744,708
New environment	2,632,219	2,645,917	2,640,648	2,611,835	2,592,148
Clinical impact	**-1,496**	**-15,118**	**-47,991**	**-104,694**	**-152,560**

and is largely preventable. Optimizing PPH prevention efforts should be paramount and would accelerate progress toward achieving SDG 3.1. WHO's 2018 Recommendations on Uterotonics for the Prevention of PPH provide a new alternative, heat-stable carbetocin, for countries to consider in helping to accelerate progress. Based on our evaluation, adoption of heat-stable carbetocin in India is expected to reduce PPH events, leading to a reduction in health care resource utilization and material cost-savings to India's public healthcare system – key supportive tenets of country achievement of SDG 3.1 and Universal Health Coverage objectives.

Health care policy makers are increasingly looking to health technology assessments to support informed programmatic and procurement decisions, including the ones related to new innovations such as heat-stable carbetocin [22]. Applying WHO's 2018 Recommendations, and considering India's public health system, the results of our assessments provide compelling rationale for country adoption of heat-stable carbetocin as a new alternative to help optimize PPH prevention efforts.

Reducing PPH events has, as a consequence, additional clinical, institutional and societal benefits. The most straight-forward are a lower number of PPH-related near-misses, post-partum complications and deaths, and a reduction in DALYs. Fewer PPH events also has the further benefit of alleviating over-burdened public health facilities, primarily by reducing the number of affected women requiring additional hospital stay, the duration of that hospital stay and the related healthcare personnel time and cost to manage their care.

The considerable savings to the Indian public health system suggested by the budget impact analysis following the uptake of heat-stable carbetocin for PPH prophylaxis would provide the opportunity to shift limited resources to complementary or other areas of health.

Use of heat-stable carbetocin also brings advantages with respect to country implementation. As refrigeration is not required and humidity has no negative consequence, it mitigates against potential weakness in cold-chain integrity – from manufacturer to in-country transport and storage or consistency in facility access to electricity – and climactic conditions, and thus can be conveniently used in any setting while maintaining its quality. Consequently, consistency in quality can lead to better real-world outcomes and, importantly, enhanced trust between provider and patient that she is getting good quality medicine.

While the heat-stability of carbetocin may be perceived as a key advantage in more remote, primary healthcare facilities where cold-chain and electricity challenges are most prevalent, this study demonstrated benefits are achieved across all levels of the public healthcare system (PHC, SHC, THC), even when conservatively assuming quality is equalized across prophylactic uterotonics. While reductions in mortality are greater in the PHC and cost savings are higher in the THC, heat-stable carbetocin lowered DALYs and costs over both oxytocin and misoprostol regardless of the setting.

Importantly, the cost-effectiveness model also shows that overall costs savings held true despite a higher acquisition cost of heat-stable carbetocin compared to oxytocin or misoprostol, and the up-front cost of any prophylactic uterotonic – heat-stable carbetocin, oxytocin or misoprostol – was not a key driver of the overall cost to address PPH. Our analysis highlights that programmatic and procurement decisions based solely on the up-front uterotonic acquisition cost would lead to a suboptimal budget decision and would be misaligned with the goal to achieve both SDG 3.1 and UHC agendas.

It should be noted that while the assessment presented in this paper was applied to India, the model can easily be adapted using country-specific inputs to assist decision makers in any LMIC.

Limitations

While providing insights into alternative programmatic and procurement decisions, our heath economic evaluation is not without limitations. Due to the lack of local sources for several aspects of uterotonic use and the influence of factors such as anemia on rates of PPH and death rates from PPH, some data inputs and assumptions may lack peer-reviewed validation. In these cases, we relied heavily on insights from Indian clinical experts. The impact of these data limitations is difficult to quantify, but sensitivity analyses suggest overall results (cost saving and improved health outcomes) are robust to uncertainty in model parameters. These data limitations also reinforce the need to improve data collection around maternal health care, and specifically around PPH as the leading direct cause of death.

The greater efficacy of heat-stable carbetocin to prevent PPH events compared to oxytocin and misoprostol was supported by the 2018 Cochrane Review U-NMA [12]. While the methodology is designed to minimize the risk, results are subject to potential bias due to differences in the included studies. When we utilized the alternative CHAMPION trial for the efficacy of heat-stable carbetocin and oxytocin, [39] the benefit of heat-stable carbetocin was reduced, but more PPH events were still avoided and total costs remained lower with heat-stable carbetocin. Regardless of the study used, the effectiveness of uterotonics on PPH is likely to differ in practice due to manufacturing, transport, storage, or climactic issues that can impact quality. For example, poor-quality misoprostol was not factored into the model despite

documented evidence of consistently poor quality. For oxytocin, while the prophylactic recommended dosage was increased to compensate for poor-quality based on behavioral practice (and thus the costs increased), we did not decrease its effectiveness. Thus, the model is likely underestimating the risk of PPH and associated costs compared with the real-world prophylactic administration of oxytocin and misoprostol. Further, studies have shown that cold-chain is not always maintained in LMICs, and thus the true costs of cold-chain are unknown and may be under-estimated.

While we indicate maternal age is an important factor in the risk of death from PPH based on Tort et al. (2015), with risk increasing by age group (<20, 20 to 35, >35), results are not provided separately by age. We chose not to investigate this given the high percentage of women in the 20 to 35 age group (over 95%) and the lack of data on other factors that might differ by age (i.e., rate of c-sections). If age-based decisions regarding use of prophylaxis is to be investigated, further efforts would be needed to collect these inputs.

Finally, the costs of certain PPH management interventions (e.g., laboratory tests and invasive procedures) were excluded from the model to allow for the greatest applicability across healthcare settings, thus likely underestimating the total medical costs to manage PPH. And, as the model only focused on direct PPH-related medical care costs to the healthcare system, additional start-up costs to the system, such as healthcare provider training on new alternatives, or out-of-pocket costs to the individual/family, were not included.

Conclusions

The cost-effectiveness and budget impact models can be used by decision makers in LMICs to assess the utility of heat-stable carbetocin as a first line alternative to prevent PPH. Despite the limitations, this model projects a favorable impact – health outcomes and economic savings – of introducing heat-stable carbetocin in India's public sector. Across all levels of the healthcare system, heat-stable carbetocin was projected to reduce the number of PPH events at a lower cost to the public healthcare system. While our findings are consistent with recent studies [40–42], to our knowledge this is the first time this has been shown in a LMIC setting using public health sector pricing for all uterotonics, including heat-stable carbetocin. Consequently, these results, based on Health Technology Assessment methodology, suggest heat-stable carbetocin could be a valuable new prophylactic uterotonic in India's efforts to prevent PPH and advance its efforts toward achievement of its SDG 3.1 and Universal Health Coverage goals.

Abbreviations

DALYs	Disability-adjusted life years
HTA	Health technology assessment
HTAIn	Health Technology Assessment in India
ICER	Incremental cost-effectiveness ratio
LMICs	Low- and middle-income countries
MMR	Maternal mortality ratio
MoHFW	Ministry of Health and Family Welfare
OWSA	One-way sensitivity analyses
PHC	Primary health center
PPH	Postpartum hemorrhage
PSA	Probabilistic sensitivity analyses
SDG	Sustainable Development Goal
SHC	Secondary health center
THC	Tertiary health center
UHC	Universal health coverage
U-NMA	Uterotonic network meta-analysis
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-023-09263-4.

Additional file 1: Table S1. Healthcare resource utilization cost inputs by healthcare center type. **Table S2.** Key* model input values for deterministic and probabilistic sensitivity analyses. **Table S3.** Breakdown of total costs per 100,000 women. **Table S4.** Incremental outcomes per woman for heat-stable carbetocin versus alternative prophylactic uterotonics by healthcare center type. **Table S5.** Scenario Analysis: Costs and health outcomes per woman for all births. **Fig S1.** Tornado diagrams for heat-stable carbetocin vs oxytocin. **Fig S2.** Tornado diagrams for heat-stable carbetocin vs misoprostol.

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Authors' contributions

J.C. contributed to the methodology, software development, and analysis. K.S. contributed to the methodology, analysis, and project supervision. C.T. contributed to the conceptualization of the project, input collection, and project supervision. J.J. contributed to the conceptualization of the project, input collection, analysis, and project supervision. All authors contributed to the writing of the manuscript and approved the final manuscript.

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Availability of data and materials

Data can be acquired from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests
John R. Cook is an employee of Complete HEOR Solutions, under contract to Merck Sharp & Dohme LLC, subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Kunal Saxena, Catharine Taylor, and Jeffrey L. Jacobs are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock or own stock options in the Company.

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