Effect of heat stable carbetocin vs oxytocin for preventing postpartum haemorrhage on post delivery hemoglobin—a randomized controlled trial.

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ABSTRACT
Objective: To compare the effect of heat-stable carbetocin 100 μg IM versus oxytocin 10 IU IM on post-delivery hemoglobin level.
Setting: Hospital based study in Southern India.
Population: Women delivering vaginally who were enrolled in the WHO CHAMPION trial in a single facility in India. WHO CHAMPION Trial was a randomized, double-blind, noninferiority trial comparing intramuscular injections of heat-stable carbetocin with oxytocin administered immediately after vaginal birth in women across 23 sites in 10 countries.
Methods: This was a nested randomized controlled trial designed to compare the effect of heat-stable carbetocin 100 μg IM versus oxytocin 10 IU IM, administered within one minute of vaginal delivery of the baby for prevention of postpartum hemorrhage, on post-delivery 48–72 h hemoglobin level, adjusted for pre-delivery hemoglobin level. 1,799 women from one hospital in India participated in this study.
Results: Pre-delivery hemoglobin and postpartum blood loss were not significantly different between carbetocin and oxytocin. Post-delivery hemoglobin, unadjusted or adjusted for pre-delivery hemoglobin, was slightly lower for carbetocin (10.09 g/dL) compared to oxytocin (10.21) (p value of 0.0432). The drop in hemoglobin was slightly higher for carbetocin, although the difference was very small (1.2 g/dL for carbetocin, 1.1 g/dL for oxytocin) (p value of .0786). The proportion of participants with a drop in hemoglobin of 2 g/dL or more, adjusted for pre-delivery hemoglobin, was higher for carbetocin (RR = 1.29, 95% CI 1.02–1.63). From the regression coefficients it can be derived that post-delivery hemoglobin, adjusted for pre-delivery hemoglobin, decreases on average 0.12 g/dL for each dL of blood lost, for the two treatments combined.
Conclusion: The present ancillary study showed that intramuscular administration of 100 μg of heat stable carbetocin can result in a slightly lower post-delivery hemoglobin, slightly higher drop and higher percentage of women having a drop of 2 g/dL or larger, compared to 10 IU of oxytocin.

Introduction

Background

Maternal mortality continues to be unacceptably high and in 2017, about 295,000 women died during and following pregnancy and childbirth. Almost all of these deaths occurred in low-resource settings, and most could have been prevented [1]. The Sustained Development Goals adopted by the United Nations in 2015 aims at improving maternal health by reducing the global maternal mortality ratio to less than 70 per 100,000 livebirths by 2030 [1,2]. Postpartum hemorrhage (PPH) is one of the major causes of maternal mortality in low- and middle-income countries. PPH affects approximately 6% of all women who give birth [2–4]. It is associated with nearly one-fourth of all maternal deaths globally and uterine atony is the most common cause of PPH [3]. PPH is commonly defined as a blood loss of 500 mL or more within 24 h after birth, while severe PPH is defined as a blood loss of 1000 mL or more within the same timeframe. The majority of deaths due to uterine atony resulting in
PPH could be avoided through the use of prophylactic good quality uterotonics during the third stage of labor and by timely and appropriate management [5]. WHO recommendations, updated in 2018, mention five effective drugs for the prevention of PPH namely oxytocin, carbetocin, misoprostol, ergometrine/methyl-ergometrine, and oxytocin with ergometrine fixed-dose combination [3,6]. Oxytocin (IM/IV, 10IU) is recommended as the uterotonic drug of choice [3]. The use of heat-stable (HS) carbetocin has been recommended for the prevention of PPH in settings where oxytocin is unavailable (or its quality cannot be guaranteed) and where the cost of HS carbetocin is comparable to other effective uterotonics [3,7,8]. HS carbetocin is a long-acting synthetic agonist analogue of the human oxytocin [9-11].

The World Health Organization conducted the WHO CHAMPION trial which was a phase III, randomized, double-blind, active controlled, multinational, multi-centre, non-inferiority trial comparing the effectiveness of HS carbetocin with oxytocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally. The study showed that HS carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 mL or the use of additional uterotonic [5,12].

Although measured postpartum blood loss has been used as the primary outcome in a number of trials assessing the efficacy of strategies for prevention and treatment of PPH, post-delivery hemoglobin and decline from pre-delivery level have been regarded as more appropriate alternatives because they are theorized to be stronger indicators of risk for shock and death than postpartum blood loss [13]. Secondary analysis of data from three multi country randomized trials done by Anger H showed that there was a correlation between the blood loss after delivery and post-partum drop in hemoglobin. The study also showed that clinically meaningful drops in hemoglobin did not occur until blood loss exceeded 1000 mL [14,15]. Mean drop in pre-to-post hemoglobin of 2 g/dL or more is considered a clinically important value to assess the correlation between blood loss and post-partum drop in hemoglobin in previous studies [13,16,17]. There are no studies assessing the effect of heat stable carbetocin for prevention of postpartum hemorrhage in low risk vaginal deliveries with post-delivery hemoglobin as the primary outcome. Even the large heat stable carbetocin trial coordinated by WHO has not incorporated post-delivery hemoglobin as an end point for assessing the efficacy of heat stable carbetocin. Hence, we conducted a nested randomized controlled study under the WHO CHAMPION Trial to compare the effect of heat-stable carbetocin 100μg IM versus oxytocin 10IU IM on post-delivery hemoglobin level in one of the participating facilities in India.

Material and methods

This is an ancillary study of the WHO CHAMPION trial which collected data on pre and post-delivery hemoglobin levels during the period of 12 months. The primary outcome was post-delivery 48–72 h hemoglobin. The secondary outcome was the proportion of women with a drop in post-delivery hemoglobin ≥2 g/dL after 48–72 h of delivery [12].

The WHO CHAMPION trial was a randomized, double-blind, non-inferiority trial comparing the effectiveness of HS carbetocin with oxytocin for the prevention of PPH after vaginal birth. The trial methods and results are described in detail elsewhere [12]. This ancillary study was conducted in one of the six participating sites in India, and it consisted of including the additional measurement of pre- and post-delivery hemoglobin to the WHO CHAMPION protocol. Design and procedures are the ones described in the main study [5,12].

After initial clinical assessment of women presenting for delivery to the KLES Dr Prabhakar Kore Charitable Hospital & Medical Research Center, Belgaum, a written informed consent was taken separately for the ancillary study along with the consent for the main trial.

Pre-delivery hemoglobin of each participant was recorded before she was randomized to the main trial. Estimation of hemoglobin was done using the HemoCue Hb 301 with the technology of absorbance measurement of whole blood at Hb/HbO2 isobestic point with a cuvette. Under aseptic conditions, 0.5 mL of the capillary blood was collected after finger prick with a sterile lancet and placed on the cuvette. The time required by the hemoglobinometer for the hemoglobin estimation was approximately 10 s. Hemoglobin values were recorded on a form specifically designed for this study.

During the second stage of labor when vaginal delivery was imminent, eligible women were randomized to receive either oxytocin 10 IU IM or HS carbetocin 100μg IM based on the random allocation sequence generated centrally at WHO Headquarters (the CHAMPION trial coordination center) using computer-generated random numbers. During the third stage of labor women received the randomly assigned...
treatment, and blood loss was measured for one hour or two hours if bleeding continued after the first hour [17].

Post-delivery hemoglobin was measured using the same standard procedure used for estimation of pre-delivery hemoglobin between 48 and 72 h postpartum.

The present study was approved by JNMC Institutional Ethics Committee for Human Subjects. The trial was registered with Clinical Trial Registry of India CTRI/2016/06/006996.

**Statistical analysis**

The main analysis was conducted with the modified intention-to-treat population (as defined in Widmer et al.) [12]. 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.

Descriptive statistics were calculated for characteristics of women and those of babies at birth. The number of participants, number of events and percentages in each category were calculated for the categorical variables. Number of participants, median and interquartile range (IQR) were calculated for the numeric variables.

Univariate analyses were conducted with the variables: pre-delivery hemoglobin, post-delivery hemoglobin, the drop from pre-delivery to post-delivery hemoglobin, and blood loss, to compare the treatments, using analysis of variance techniques. The statistical distribution of the variables was examined to decide whether a transformation was needed. The difference of means was used if the distribution was close to normal. In the case of blood loss, the distribution was asymmetric and the logarithmic transformation was used.

The primary outcome, post-delivery hemoglobin, was analyzed using analysis of covariance to compare treatments, with pre-delivery hemoglobin as covariate to adjust the post-delivery hemoglobin for possible differences in baseline values (Model 1). Analysis of covariance is the preferred technique compared to the analysis of post-pre-difference [18,19], and it is a special case of regression analysis. Adjusted means of differences in post-delivery hemoglobin were calculated, with 95% confidence intervals.

The analysis of covariance in Model 2 was extended to assess the association of post-delivery hemoglobin and blood loss volume between the treatments, by including a term for blood loss in the model (Model 2). This association was further explored by including an interaction term of blood loss by arm in the model in order to allow the treatment regression lines to have different slopes (Model 3). The association between post-delivery hemoglobin and blood loss was quantified by the treatment-specific regression coefficients.

The proportion of women with a drop in post-delivery hemoglobin of 2 g/dL or more from pre-delivery hemoglobin was calculated for each treatment and compared using logistic regression and relative risk (RR) with 95% confidence intervals and risk difference with 95% confidence intervals. Both unadjusted and adjusted analysis for pre-delivery hemoglobin were conducted.

**Results**

The Belgaum site participated in the main study-CHAMPION Trial and recruited 1799 women for this sub-study. The trial profile is shown in Figure 1. After randomization, two women underwent cesarean section in each group. After excluding the missing values, the participants included in final analysis were 890 in the HS carbetocin group and 889 in the oxytocin group.

Baseline characteristics of women at trial entry, characteristics of women at labor and characteristics of babies at birth were similar for the two treatment groups (Table 1).

The mean pre-delivery hemoglobin and median post-partum blood loss as shown in Table 2 were similar across the treatment groups. For post-delivery hemoglobin unadjusted analysis the mean was slightly lower for carbetocin compared to oxytocin (0.128 g/dL lower, p-value = .0432). The drop in hemoglobin between pre-delivery and post-delivery was slightly higher for carbetocin (p-value = .0786). The results of the adjusted analyses for post-delivery hemoglobin (Model 1) are shown in Table 2. The adjustment for pre-delivery hemoglobin showed similar results to the unadjusted analysis (similar point estimate for the difference between treatments in post-delivery hemoglobin means and p-value = .0334). Additionally, adjusting for blood loss (Model 2) did not change the results.

From Model 3 (see Appendix Table A3) it can be seen that the decrease in post-delivery hemoglobin for each dL of blood lost, adjusted for pre-delivery hemoglobin, is not significantly different between carbetocin and oxytocin (p-value = .2171 for the interaction blood loss by treatment group). Then Model 2 (see Appendix Table A2) can be used to estimate the
Table 1. Characteristics of women at trial entry and at labor, and of babies at birth.

| Maternal characteristics | Carbocetin (N = 897) | Oxytocin (N = 898) |
|--------------------------|----------------------|--------------------|
| Age- yr                  | 23                   | 23                 |
| Median                   |                      |                    |
| Interquartile range      | 5                    | 5                  |
| Nulliparous – number (%) | 468 (52.2)           | 493 (54.9)         |
| Previous miscarriages – number (%) | 102 (11.4) | 119 (13.3) |
| CS in previous deliveries* – number (%) | 21 (4.9) | 26 (6.5) |
| Gestational age (completed weeks) – n | 897 | 898 |
| Median                   | 39                   | 39                 |
| Interquartile range      | 2                    | 2                  |
| Labor induced – number (%) | 155 (17.3)           | 142 (15.8)         |
| Labor augmented – number (%) | 167 (18.6)           | 160 (17.8)         |
| Instrument-assisted vaginal birth – number (%) | 34 (3.8) | 34 (3.8) |
| Perineal trauma leading to suture – number (%) | 829 (92.4) | 833 (92.8) |
| Occupation:              |                      |                    |
| Home-maker- number (%)   | 883 (98.4)           | 884 (98.4)         |
| Education:               |                      |                    |
| Illiterate- number (%)   | 35 (3.9)             | 47 (5.2)           |
| Fetal characteristics    |                      |                    |
| Baby alive- number (%)   | 849 (94.6)           | 850 (94.7)         |
| Sex male* – number (%)   | 446 (49.7)           | 453 (50.5)         |
| Birthweight (grams) – n  | 897                  | 898                |
| Median                   | 2800                 | 2800               |
| Interquartile range      | 610.0                | 600.0              |

*Two values are missing for CS and Postpartum hemorrhage in previous pregnancies in the Oxytocin group.

*One missing value for sex of baby in the Oxytocin group.
aggregated decrease in post-delivery hemoglobin for each dL of blood lost, given by the regression coefficient of blood loss, as 0.12 g/dL (95% CI 0.07–0.16).

A drop of ≥2 g/dL in hemoglobin from pre-delivery to post-delivery after 48–72 h of delivery was seen in 27.9% of women in carbetocin group compared to 24.1% in the oxytocin group as shown in Table 3. The relative risk of having this event among women receiving carbetocin, compared to women receiving oxytocin, was 1.16 (95% CI 0.99–1.36) in the unadjusted analysis, not attaining significance at 5% (p-value = .0682). When adjusted for pre-delivery hemoglobin, the relative risk was 1.29 (95% CI 1.02–1.63), significant at 5% (p-value = .0337).

**Discussion**

In the present ancillary study, we were able to assess the effect of HS carbetocin compared to that of oxytocin on the post-delivery (48–72 h) hemoglobin and on the drop in hemoglobin between pre-delivery and post-delivery hemoglobin. There was a drop in hemoglobin between pre-delivery and post-delivery of the order of 1 g/dL, and even though the difference in this drop between HS carbetocin (1.2 g/dL) and oxytocin (1.1 g/dL) was close to significance (p-value = .0786), the difference was clinically unimportant. Post-delivery hemoglobin, adjusted for pre-delivery hemoglobin and blood loss, was marginally lower for HS carbetocin compared to oxytocin (0.13 g/dL lower), statistically significant but not clinically relevant. Our study showed that the decrease in post-delivery hemoglobin for each dL of blood lost adjusted for pre-delivery hemoglobin was not significantly different between two groups, and it was on average 0.12 g/dL for each dL of blood lost. The overall negative association between post-delivery hemoglobin and blood loss was statistically significant (p < .0001). The drop in post-delivery hemoglobin ≥2 g/dL after 48–72 h of delivery adjusted for pre-delivery hemoglobin was higher for carbetocin (p value = .0337) although it was not clinically relevant.

A study done by Larciprete et al. comparing the use of carbetocin versus oxytocin in cesarean section with high risk of post-partum hemorrhage showed that the post-partum drop in hemoglobin after 2 h and 24 h was similar in both the groups [16]. Another study done by Mark Boucher showed similar results wherein no significant difference was seen in the drop in hemoglobin and hematocrit values between the two groups receiving carbetocin and oxytocin after vaginal delivery [20]. In the parent CHAMPION trial there was no significant difference between carbetocin and oxytocin for blood loss 500 mL or more and for blood loss 1000 mL or more (Widmer et al.; Table 2) [12]. We did not estimate these outcomes in the

| Table 2. Mean pre-delivery and post-delivery hemoglobin, mean drop in hb and median postpartum blood loss – univariate unadjusted analysis. |
| Outcome | Carbetocin | Oxytocin | Difference or ratio (95% CI) | p-value |
|---------|------------|----------|-----------------------------|---------|
| Outcome | N = 890 | N = 889 | | |
| Pre- delivery Hemoglobin (g/dL, mean, difference) | 11.3 | 11.3 | −0.014 (−0.136 to 0.107) | .8169 |
| Post- delivery Hemoglobin (g/dL, mean, difference) | 10.09 | 10.21 | −0.128 (−0.251 to −0.004) | .0432 |
| Drop in Hb (g/dL, mean – median, difference) | 1.2 | 1.1 | 0.117 (−0.013 to 0.248) | .0786 |
| Postpartum blood loss (mL, median, ratio) | 160.4 | 163.2 | 0.98 (0.92–1.05) | .214 |

*Analysis of variance. **Analysis of covariance to compare treatments, with pre-delivery hemoglobin as covariate to adjust the post-delivery hemoglobin for possible differences in baseline values. ***Analysis of covariance to compare treatments, with pre-delivery hemoglobin and blood loss as covariates.

| Table 3. Secondary outcome: proportion of women with a drop in post-delivery hemoglobin ≥2 g/dL after 48–72 h of delivery (mITT Population). |
|----------------------------------|--------|--------|----------------|--------|
| Outcome                          | CARB   | OXY    | Risk Difference % | Lower CL | Upper CL |
| Drop in Hb ≥ 2 g/dL unadjusted   | 248    | 890    | 27.9           | 214     | 889      |
| Drop in Hb ≥ 2 g/dL adjusted for pre-delivery Hb | – | 1.29 | 1.02 | 1.63 | .0337 | 3.89 | .016 | 7.61 |

Results from logistic regression, with the log link to produce relative risks.
present substudy because of lack of power. The comparison of carbetocin and oxytocin in terms of continuous blood loss in the present study showed no significant difference in blood loss (p-value = .6214), which is consistent with CHAMPION results.

Despite the slightly higher, but clinically insignificant, drop in post-delivery hemoglobin for HS carbetocin compared to oxytocin, the former offers advantage in being heat stable. This should be interpreted keeping in mind the study implementation, where oxytocin was maintained in the ideal conditions. The results would have been different for oxytocin if it was used under routine field conditions where studies have reported unsatisfactory real-world efficacy due to sensitivity to heat and quality issues of the drug [21]. Delayed diagnosis and treatment can lead to hypovolemic shock in women with severe postpartum hemorrhage. Hence, accurate measurement of blood loss and timely diagnosis and management can prevent avoidable morbidity and mortality associated with cases of severe post-partum hemorrhage [14]. Based on results from the present study, measurement of drop in hemoglobin might be eventually used as a proxy for post-partum blood loss. The use of heat stable carbetocin would be a boon for prevention of post-partum hemorrhage in peripheral regions of low and middle-income countries where constant maintenance of cold temperature for oxytocin is a difficulty.

Conclusion

Post-delivery hemoglobin was slightly lower for carbetocin compared to oxytocin and the drop in hemoglobin was slightly higher for carbetocin. The proportion of participants with a drop in hemoglobin of 2 g/dL or more, was higher for carbetocin. However, the magnitude of these differences was not clinically relevant. The present study also showed that there is a decrease in post-delivery hemoglobin with blood loss which was not significantly different between carbetocin and oxytocin groups. These data inform care of women in settings with fragile cold chains.

Acknowledgement

We gratefully acknowledge the contributions of all the study investigators and data collectors towards the implementation of this study.

Authors’ contributions

SSV conceived of the manuscript and wrote the first draft with input from MSS, SSG, GP, JFC, AMG and MW. SSV, SSG, MM, YVP, AR, MSS and SSG oversaw study implementation, data collection and quality monitoring. GP and JFC performed the statistical analyses. All authors reviewed and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

The main trial was supported by funding from MSD, through its MSD for Mothers program and is the sole responsibility of the authors. MSD for Mothers is an initiative of Merck & Co., Inc., Kenilworth, NJ, U.S.A. The study was funded by KLE Academy of Higher Education & Research.

Clinical trial registration

The trial was registered with Clinical Trial Registry of India CTRI/2016/06/006996.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available in the World Health Organization repository. The link to datasets can be requested to Mariana Widmer at widmerm@who.int

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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**Appendix**

**Table A1.** Results from the fit of Model 1: Parameter Estimates (hbpre: Pre-delivery hemoglobin).

| Term                | Estimate   | Std Error | t Ratio | Prob>|t| |
|---------------------|------------|-----------|---------|-----|---|
| Intercept           | 5.168484   | 0.240833  | 20.84   | <.0001* |
| hbpre               | 0.4402135  | 0.021763  | 20.23   | <.0001* |
| Arm [Carbetocin]    | -0.060572  | 0.028455  | -2.13   | 0.0334* |

**Table A2.** Results from the fit of Model 2: Parameter Estimates (hbpre: Pre-delivery hemoglobin; bloss: Postpartum blood loss).

| Term                | Estimate   | Std Error | t Ratio | Prob>|t| |
|---------------------|------------|-----------|---------|-----|---|
| Intercept           | 5.4463417  | 0.25103   | 21.70   | <.0001* |
| hbpre               | 0.4357607  | 0.021598  | 20.18   | <.0001* |
| Arm [Carbetocin]    | -0.062997  | 0.028223  | -2.23   | 0.0257* |
| bloss               | -0.001169  | 0.000211  | -5.55   | <.0001* |

*Decrease in post-delivery hemoglobin for each mL of blood lost: 0.001169 x 100 = 0.12g/dL.

**Table A3.** Results from the fit of Model 3: Parameter Estimates (hbpre: Pre-delivery hemoglobin; bloss: Postpartum blood loss; bloss*arm: interaction of Postpartum blood loss by Arm); see footnote* for derivation of decrease in post-delivery hemoglobin for each mL of blood lost.

| Term                | Estimate   | Std Error | t Ratio | Prob>|t| |
|---------------------|------------|-----------|---------|-----|---|
| Intercept           | 5.468795   | 0.251649  | 21.73   | <.0001* |
| hbpre               | 0.4337769  | 0.021655  | 20.03   | <.0001* |
| Arm [Carbetocin]    | -0.062997  | 0.028223  | -2.23   | 0.0257* |
| bloss               | -0.001169  | 0.000211  | -5.53   | <.0001* |
| bloss*arm[Carbetocin]| 0.0002607  | 0.000211  | 1.23    | 0.2171 |

*Decrease in post-delivery hemoglobin for each mL of blood lost: 0.12 g/dL.

(Carbetocin: 0.0002607–0.001166 = -0.0009053g/dL for each mL = -0.09053g/dL for each mL; Oxytocin: -0.0002607 to 0.001166 = -0.0014267g/dL for each mL = -0.14267g/dL for each mL)
Figure A1. Plot of post-delivery hemoglobin (g/dL) versus blood loss (mL), by treatment.