ORIGINAL ARTICLE

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

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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 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 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

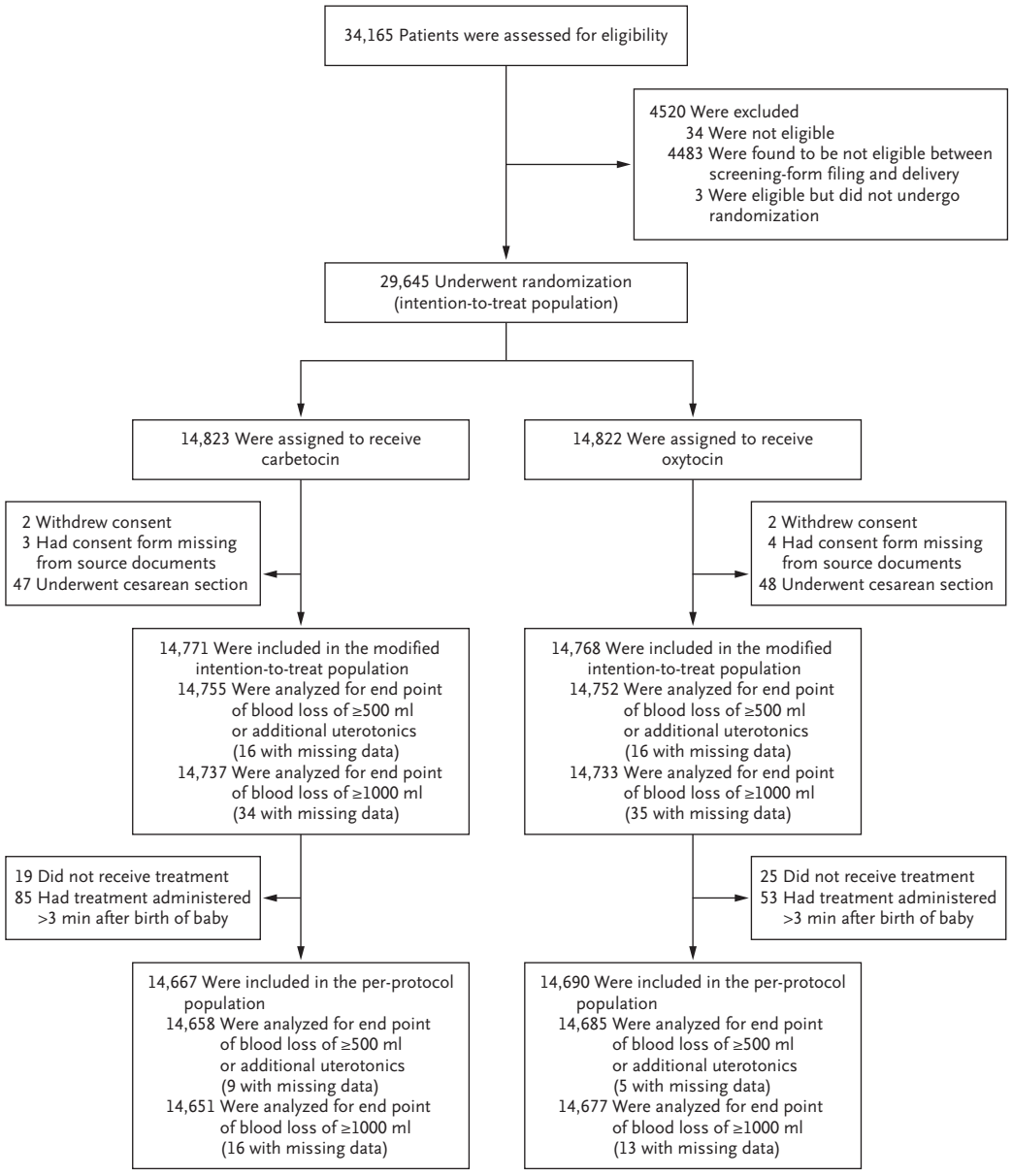

Figure 1. Trial Profile and Modified Intention-to-Treat and Per-Protocol Populations.
Informed consent was sought at hospital admission (see the protocol).

(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

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-

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)	—

* 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. All the P values that were 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.

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-

‡ 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.

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

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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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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