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

C H A M P I O N
Carbetocin HAeMorrhage PreventION trial
Declaration of interest

- This presentation was prepared by WHO (HRP/RHR)
- Nothing of value is accepted from Ferring Pharmaceuticals for or in relation to the presentation by collaborating investigators, including but not limited to honoraria, travel expenses, meals, hotel expenses etc.
- Merck for Mothers provides financial support to WHO for Trial related activities, including presentations at symposia or congresses.
Severe bleeding is the main cause of maternal mortality

WHAT ARE PREGNANT WOMEN DYING FROM?

- **28%**
  Pre-existing medical conditions exacerbated by pregnancy (such as diabetes, malaria, HIV, obesity)

- **3%**
  Blood clots

- **8%**
  Abortion complications

- **9%**
  Obstructed labour and other direct causes

- **27%**
  Severe bleeding

- **14%**
  Pregnancy-induced high blood pressure

- **11%**
  Infections

73% due to postpartum haemorrhage
Oxytocin

First choice drug for preventing PPH

- Requires a consistent cold chain to maintain effectiveness
- Is unable to reach women in facilities that lack (consistent) cold-chain capability
- Adds burden & complication to already stretched cold-chain infrastructure
- There are concerns about its quality

WHO recommendations for the prevention and treatment of postpartum haemorrhage

2012
### Why heat stable carbetocin (HSC) might be important?

**Carbetocin in the market since many years**
- 1st approved in 1997
- Registered in >80 countries for PPH prevention mainly in CS births
- Cumulative post-marketing exposure >10.5 million women, mainly CS, IV

**Safety profile similar to oxytocin**
- Nausea
- Feeling of warmth
- Chills, pain
- Headache, tremor
- Hypotension

**Heat Stable Carbetocin**
- Only differences in excipients (GRAS - generally recognized as safe)
- Stable for 48 months at 30°C; 6 months at 40°C
Uterotonic agents for preventing PPH: a network meta-analysis

- Which uterotonic drug is most effective to prevent PPH, with a favourable side-effect profile?

- Included trials:
  - 100 trials (76,894 women) – Blood loss ≥500 mL
  - 90 trials (78,014 women) – Blood loss ≥1000 mL

- Conclusions:
  - All drugs are effective when compared with placebo
  - Most effective drugs for all blood loss outcomes
    - 1st ranked: Syntometrine (ergometrine + oxytocin)
    - 2nd ranked: Carbetocin
    - 3rd ranked: Oxytocin + Misoprostol combination (OxyMiso)
  - Worst drugs for side effects: syntometrine, OxyMiso
  - Carbetocin vs oxytocin: very low quality due to high risk of bias, inconsistency and imprecision (small trials)
Heat Stable Carbetocin is a promising agent and deserves to be researched more rigorously.
A unique public private collaboration to prevent PPH

Phase 3 Trial  
PPH Guidelines EML  
Institutional, Country-level advocacy

Catalyst, Trial Funding  
Scientific & Business Expertise  
Support introduction & uptake planning & advocacy

Product expertise & clinical trial supply  
Register in identified LMI countries  
Manufacture & provide access @ affordable, sustainable access price
The Collaboration: End-to-End Thinking

- WHO CHAMPION trial

- Regulatory Strategy
  - WHO Guidelines
  - Essential Medicines List
  - WHO Pre-Qualification
  - Country regulatory approval

- Manufacturing & Supply
  - Quality assured product (GMP)
  - Unique packaging; Traceability
  - Capacity to meet eligible LMIC demand
  - Route-to-Market

- Product Introduction
  - Stakeholders
  - Value Proposition & Positioning
  - Affordability
  - Access
  - Communications
The WHO CHAMPION trial

“A phase III, randomized, double-blind, active, controlled, multinational, multicentre, non-inferiority trial using heat-stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally”

P: women, third stage of labour, vaginal birth
I: heat-stable carbetocin 100 µg IM
C: oxytocin 10 IU IM
O: blood loss ≥ 500 mL or additional uterotonics
  blood loss ≥ 1000 mL

Trial was registered in the
Australian New Zealand Clinical
Trials Registry
(ACTRN12614000870651)
Trial oversight

- HRP/RHR oversaw the conduct of the trial.
- Heat stable carbetocin was provided by Ferring Pharmaceuticals and oxytocin by Novartis free of charge.
- 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.
- Trial initiation, monitoring, and closure and safety monitoring at the trial sites were provided by IQVIA (formerly Quintiles IMS–Quintiles).
- MSD and Ferring provided input into the protocol and comments on the manuscript. 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.
Participating countries and sample size

30,000 women
23 hospitals
10 countries
Eligibility criteria

Inclusion criteria

- Singleton pregnancy
- Planned to have a vaginal birth
- Cervical dilatation ≤ 6 cm at the moment of giving written informed consent

Exclusion criteria

- Not capable of giving informed consent
- Planned caesarean section
- Birth considered an abortion
- Allergies to the medicinal products used in the trial
- Serious cardiovascular, hepatic or renal disorder or epilepsy.
Interventions

• HS Carbetocin 100 μg/mL IM (investigational drug undergoing trial)
• Oxytocin 10 IU IM (comparator drug)

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.
Outcomes

Primary

- 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.
- 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.

Secondary

- proportion of women with blood loss ≥500
- Blood loss in ml
- proportion of women receiving additional uterotonics
- proportion of women receiving additional uterotonics up to time of discharge
- proportion of women receiving blood transfusion up to time of discharge
- proportion of women with manual removal of placenta up to time of discharge
- proportion of women having additional surgical procedures (e.g. 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.
- proportion of maternal death.
- proportion of women with composite outcome of maternal death or severe morbidity (admission to intensive care unit, hysterectomy, blood loss of two liters or more, uterine inversion) up to time of discharge.
- 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).
Trial procedures

- Management of the third stage of labour followed WHO PPH recommendations
- Intervention administered immediately after the birth of the baby.
- Blood loss collected with a plastic drape for one hour or two hours postpartum, if the bleeding continued beyond one hour.
- Participation in the trial ended at hospital discharge or if the woman was transferred to a higher care unit.
Participant flow

HS carbetocin n=14823

Oxytocin n=14822
Results

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Conclusions

- HS carbetocin is non-inferior to oxytocin for prevention of blood loss ≥500 mL or additional uterotonic use whereas non-inferiority for blood loss ≥1000 mL is not demonstrated due to low event prevalence.

- No significant differences were found between the two groups with regard to secondary outcomes or 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 haemorrhage.
Next steps

- WHO PPH recommendations are being updated (2018 4th quarter)

- If HS carbetocin is recommended for the prevention of PPH:
  - request to include HS carbetocin in the EML
  - Country-level activities to scale up access to HS carbetocin
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