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Randomised controlled trial

Intramuscular oxytocin versus Syntometrine® versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth: a randomised double-blinded clinical trial of effectiveness, side effects and quality of life

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Objective To compare intramuscular oxytocin, Syntometrine® and carbetocin for prevention of postpartum haemorrhage after vaginal birth.

Design Randomised double-blinded clinical trial.

Setting Six hospitals in England.

Population A total of 5929 normotensive women having a singleton vaginal birth.

Methods Randomisation when birth was imminent.

Main outcome measures Primary: use of additional uterotonic agents. Secondary: weighed blood loss, transfusion, manual removal of placenta, adverse effects, quality of life.

Results Participants receiving additional uterotonics: 368 (19.5%) oxytocin, 298 (15.6%) Syntometrine and 364 (19.1%) carbetocin. When pairwise comparisons were made: women receiving carbetocin were significantly more likely to receive additional uterotonics than those receiving Syntometrine (odds ratio [OR] 1.28, 95% CI 1.08–1.51, $P = 0.004$); the difference between carbetocin and oxytocin was non-significant ($P = 0.78$); Participants receiving Syntometrine were significantly less likely to receive additional uterotonics than those receiving oxytocin (OR 0.75, 95% CI 0.65–0.91, $P = 0.002$). Non-inferiority between carbetocin and Syntometrine was not shown. Use of Syntometrine reduced non-drug PPH treatments compared with oxytocin (OR 0.64, 95% CI 0.42–0.97) but not carbetocin ($P = 0.64$). Rates of PPH and blood transfusion were not different. Syntometrine was associated with an increase in maternal adverse effects and reduced ability of the mother to bond with her baby.

Conclusions Non-inferiority of carbetocin to Syntometrine was not shown. Carbetocin is not significantly different to oxytocin for use of additional uterotonics. Use of Syntometrine reduced use of additional uterotonics and need for non-drug PPH treatments compared with oxytocin. Increased maternal adverse effects are a disadvantage of Syntometrine.

Keywords Postpartum haemorrhage, prevention, uterotonic.

Tweetable abstract IM carbetocin does not reduce additional uterotonic use compared with IM Syntometrine or oxytocin.

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Introduction

Postpartum haemorrhage (PPH) is the loss of ≥500 ml blood from the genital tract after childbirth.[1] PPH remains the most common cause of direct maternal death globally,[2] and is mostly related to uterine atony.[3] Oxytocin, Syntometrine® (a fixed dose combination of oxytocin/ergometrine; Alliance Pharmaceuticals, Chippenham, UK) and carbetocin are uterotonic agents employed to prevent atony and PPH.

Clinicaltrials.gov registration NCT02216383

Oxytocin requires cold-chain storage,[4] which can be difficult in low- and middle-income settings. Syntometrine is the most commonly used uterotonic for PPH prevention in some settings,[5] even though its use is associated with maternal hypertension, nausea and even maternal death.[6] Carbetocin is now heat-stable but can be more expensive than oxytocin.[4]

Recent robust studies have compared different uterotonics[7] and different oxytocin administration routes,[8] and there has been a network meta-analysis of different uterotonics.[9] However, no clinical trial has directly compared intramuscular oxytocin, Syntometrine and carbetocin for prevention of PPH after vaginal birth, including quality of life measurement.

Methods

Trial design, conduct and oversight

The IMox Study was a multicentre, double-blind randomised active-controlled trial comparing intramuscular oxytocin, Syntometrine and carbetocin for the prevention of primary postpartum haemorrhage after vaginal birth. Participants were randomised to three parallel arms.[10]

The trial was approved by the South Central–Oxford B Research Ethics Committee, the Medicines and Healthcare products Regulatory Agency and the Health Research Authority in the UK with oversight by North Bristol NHS Trust Research and Innovation Department.

An external Data Monitoring Committee (DMC) provided independent oversight and an independent statistician provided a blinded report to the DMC partway through recruitment, focusing on data quality, recruitment, safety and completeness of databases. There were no pre-specified stopping guidelines. Study end-date was the time when sample size was reached for the number of randomised participants providing primary outcome data. Ferring Pharmaceuticals funded the trial medication and blinding.

Aims

The primary study aims were to determine whether:

- Intramuscular (IM) carbetocin is as effective as IM Syntometrine
- IM carbetocin is more effective than IM oxytocin
- IM Syntometrine is more effective than IM oxytocin

For the primary outcome measure, a non-inferiority comparison was made between carbetocin and Syntometrine because fewer maternal adverse effects may make carbetocin a better option. Superiority comparisons were made between carbetocin and oxytocin, and Syntometrine and oxytocin.

The secondary study aims were to determine whether:

- Carbetocin is associated with fewer adverse effects than Syntometrine and oxytocin
- Choice of uterotonic agent affects maternal quality of life in the first two postnatal weeks

Trial participants

Women planning a vaginal birth were recruited from six maternity units from two regions in England. Start dates were staggered by 2 months.

Women aged 18 years or more with a spontaneous or assisted vaginal birth of a live singleton baby at ≥24 weeks of gestation were eligible. Patient Information Leaflets were provided to all pregnant women when attending an anomaly ultrasound scan at a recruiting site during the study period. Stickers on the front of maternity notes indicated who had received a leaflet. Anyone missed was opportunistically given a leaflet at subsequent visits. Women were recruited and consented in the antenatal period. When approached, women were given the time they felt necessary to consider their options. Women were not approached where there was any distress that may compromise capacity. Women were not eligible for recruitment once they were in established labour (≥4 cm cervical dilatation). Exclusion criteria included hypertension, antepartum haemorrhage, suspected placental abruption, maternal coagulation disorder, women who would decline blood products, epilepsy, and contraindication to any of the study drugs. All participants provided written consent.

Randomisation, allocation and blinding

A computer-generated drug allocation sequence was created by an independent statistician, with an assignment ratio of 1:1:1 and block size of nine, stratified by site. All three uterotonics were provided in identical 1-ml ampoules containing 1 ml of uterotonic. Ampoules were blinded by use of snapper tops and opaque labels, with boxes labelled according to the allocation sequence (see Supplementary material, Figure S1). The carbetocin used was not the heat-stable formulation, as this was not available at study onset. Heat-stable carbetocin varies from the non-heat-stable formulation only in its excipients.[7] All study drugs were stored in refrigerators. Women were randomised when vaginal birth was imminent with assignment to the next consecutively numbered box by the midwife caring for the participant. All clinical staff (outcome assessors), researchers and participants remained blinded until data lock after study closure.

Interventions

A single intramuscular injection of the allocated uterotonic (10 IU oxytocin, 500 μg/5 IU Syntometrine or 100 μg carbetocin) was administered immediately after clamping of the umbilical cord, and before expulsion of the placenta. The intervention was withheld if the participant was no longer eligible after randomisation (e.g. emergency

caesarean section or hypertension), or if consent was withdrawn. Once there was no further concern about ongoing bleeding following delivery of the placenta, blood and blood-soaked materials were collected and weighed using digital scales. Dry weights were subtracted to measure blood loss. Blood pressure was measured at 1 and 2 hours postdelivery.

Participants completed a maternal adverse effects questionnaire at 2 hours postdelivery, and an EQ-5D-5L health-related quality of life questionnaire on days 1 and 14 postdelivery. Women recruited before commencement of the latent phase of labour also completed an antenatal EQ-5D-5L questionnaire. Trial participation ended at the 14-day postnatal follow up.

Primary and secondary outcomes

The primary outcome measure was the proportion of women receiving additional uterotonics after administration of the study drug.[10] Staff were briefed, in training sessions, to administer additional uterotonics only when the uterus was inadequately contracted, with ongoing vaginal bleeding.

Secondary outcome measures included: weighed blood loss (ml), duration of third stage of labour, transfusion of blood products, use of other 'non-drug' measures to treat PPH (examination under anaesthetic/intrauterine balloon/uterine compression suture/interventional radiology) and maternal blood pressure at 1 and 2 hours postdelivery.

Participant-reported outcomes (by questionnaire at 2 hours postdelivery) included nausea, vomiting, headache, dizziness, abdominal pain, and whether these symptoms adversely affected their ability to bond with/care for their baby in the first two postnatal hours. The question relating to ability to bond was binary (yes/no). Health utility scores were calculated from EQ-5D-5L questionnaires antenatally, and on days 1 and 14 postdelivery.

Other data for PPH risk factors[1] were also collected, including mode of birth, ethnicity, pyrexia in labour and length of labour, to allow for adjustment of the results and analysis.[10]

The trial protocol was first registered on Clinicaltrials.gov in August 2014 and recruitment commenced in February 2015. The DMC reported in October 2017. The trial completed in October 2018. One of the recommendations of the DMC was the clarification of timescales relating to some outcomes. In response to this, outcome definitions were clarified in the protocol and online at clinicaltrials.gov in July 2018. Neither the outcomes themselves nor their collection method were changed. Epilepsy was added as an exclusion criteria 3 months into trial recruitment in response to the listing of epilepsy as a contraindication to the use of carbetocin in the Summary of Product Characteristics. This was approved by the Medicines and Healthcare products Regulatory Agency and Research Ethics Committee.

A Core Outcome Set for trials investigating postpartum haemorrhage was published after our study had finished recruiting.[11]

Patient involvement

A Maternity Service User Panel contributed to the study design, and reviewed the recruitment process, Patient Information Leaflet and maternal adverse effects questionnaire early in trial development, to optimise participant experience and relevance. Positive feedback was received about the inclusion of maternal bonding data. Changes instigated included midwives reading postnatal questionnaires out loud if participants did not wish to read at 2 hours postdelivery.

Sample size

The sample size calculation was based on weighted (for study size) mean prevalence, estimated by pooling of prior available data for the primary outcometaken from studies of intramuscular uterotonic drugs after vaginal birth:[12–17] use of additional uterotonics of 19.1% oxytocin, 15.2% Syntometrine and 11.5% carbetocin.

Sample size was chosen to ensure equal sample sizes across pairwise comparisons, and for the non-inferiority comparison and the two superiority comparisons to have >80% power. Assuming a non-inferiority margin of 1 and 95% power for the comparison between carbetocin and Syntometrine, 1904 participants were required per arm. Using the same number of participants in the oxytocin arm (total sample size of 5712), a four-point difference between oxytocin and Syntometrine could be detected with 88% power ($\alpha = 0.05$), and an eight-point difference between oxytocin and carbetocin with 99% power ($\alpha = 0.05$).

Attrition between randomisation (birth imminent) and administration of the study uterotonic (immediately after birth) was initially predicted to be 10%, and the sample size was inflated to 6285 participants in early protocols. When actual attrition was found to be less than 0.5%, this inflation was removed, and the required sample remained at 5712.

Statistical analysis

The intention-to-treat (ITT) population includes all participants randomised. Those that received a study drug form the modified ITT population (mITT). Some participants did not receive the Interventional Medicinal Product that they were originally assigned to. In the mITT analyses, these participants were analysed according to their original randomisation. In the Per Protocol (PP) analyses, they were analysed according to the uterotonic received.

We present the primary outcome results reported by randomised arm for the mITT population. In supplementary analyses, we report results PP (see Supplementary material, Tables S1–S5). Sensitivity analysis used the ITT population.

For the primary outcome we used an omnibus test for difference in proportions receiving additional uterotonic drugs, using the chi-square test of association. Statistical significance was two-sided $P < 0.05$. The chi-square test of association was used to examine superiority of Syntometrine versus oxytocin, and carbetocin versus oxytocin, with sample proportions as point estimates and the Pearson chi-square method to create confidence intervals for differences in proportions. The non-inferiority margin described in the original study protocol was further clarified on the recommendation of the Data Monitoring Committee after study commencement. The non-inferiority margin is 1 percentage point, as detailed in the protocol publication.[10] In the comparison between carbetocin and Syntometrine, non-inferiority was declared if the upper limit of the two-sided 95% CI for the proportion receiving additional uterotonics was less than the non-inferiority margin of 1 percentage point.

A Bonferroni adjustment was also made using a two-sided 98.3% confidence interval, to account for a three-way comparison. Both sets of confidence intervals are presented for the primary outcome data.

Analyses for all secondary outcomes were conducted only for superiority, using an appropriate omnibus test. The secondary outcome 'weighed estimated blood loss (ml)' was categorised (<500 ml, ≥500 ml, ≥1000 ml, ≥2000 ml) for analysis. Secondary outcomes were not adjusted for multiplicity.

An a priori designated sensitivity analysis was performed using the ITT group. Missing primary outcome data were substituted with an assumption that the rate of additional uterotonic drugs required was any value between 10 and 25%, covering any rate likely to be encountered in clinical practice.

The primary outcome was adjusted for known PPH risk factors including induction of labour, body mass index and previous PPH using multivariable logistic regression.[1] The same was done for the outcome of PPH ≥500 ml.

Health states generated from the EQ-5D-5L were valued from the EQ-5D-3L preference utility weights for the UK population using Van Hout's crosswalk method.[18] All analyses were conducted in IBM SPSS Statistics (IBM, Armonk, NY, USA).

Results

Participants

A total of 5929 women were recruited and randomised from six maternity units between February 2015 and August 2018 (Figure 1); of these, 212 became ineligible after randomisation and did not receive a study drug and 5717 received a study drug and were included in the mITT analyses.

Fifty-one participants (15 oxytocin, 16 Syntometrine, 14 carbetocin) did not receive the drug they were first randomised to (Figure 1); randomisation occurred when birth was believed imminent, but the uterotonic was then discarded after a longer than anticipated second stage of labour (the blinded Interventional Medicinal Product required 'immediate' administration, as per the Summary of Product Characteristics of non-heat-stable carbetocin.) For these participants, the next consecutively numbered uterotonic was administered. Thirty-four participants (10 oxytocin, 14 Syntometrine, 14 carbetocin) were involved in a protocol breach (Figure 1). The remaining 5638 participants were included in the PP analyses. Maternal characteristics at baseline and characteristics of babies at birth were similar between the three groups (Table 1).

Primary outcome

In the mITT population, primary outcome data were missing for four participants (0.2%) in the oxytocin arm and two participants (0.1%) in the carbetocin and Syntometrine arms (Table 2).

The use of additional uterotonics differed by 3.54 percentage points between the carbetocin and Syntometrine arms (95% CI 1.14–5.93%). With our pre-specified non-inferiority margin of 1%, non-inferiority of carbetocin to Syntometrine was therefore not shown, as the upper limit of the confidence interval is >+1 (see Supplementary material, Figure S2). Women in the carbetocin arm were more likely to receive additional uterotonics than those in the Syntometrine arm (odds ratio [OR] 1.28, 95% CI 1.08–1.51, $P = 0.004$).

There was a very small, non-significant difference of 0.36% in the use of additional uterotonic drugs between the oxytocin and carbetocin arms (95% CI −2.87 to 2.15%). Women in the carbetocin arm were no more likely to receive additional uterotonic drugs than those in the oxytocin arm (OR 0.98, 95% CI 0.83–1.15, $P = 0.78$).

There was a 3.90% difference in use of additional uterotonics between the Syntometrine and oxytocin arms (95% CI −6.31 to −1.49%). Women randomised to Syntometrine were less likely to receive additional uterotonics than those randomised to oxytocin (OR 0.75, 95% CI 0.65–0.91, $P = 0.002$). Bonferroni correction did not affect the conclusions.

In a sensitivity analysis, we included the primary outcome data for all women in the ITT analysis but excluded from the mITT analyses and PP analyses. The data were systematically imputed with an assumed need for additional uterotonic drugs in the range of 12–25%. Over all of these combinations, the same overarching conclusion was of no

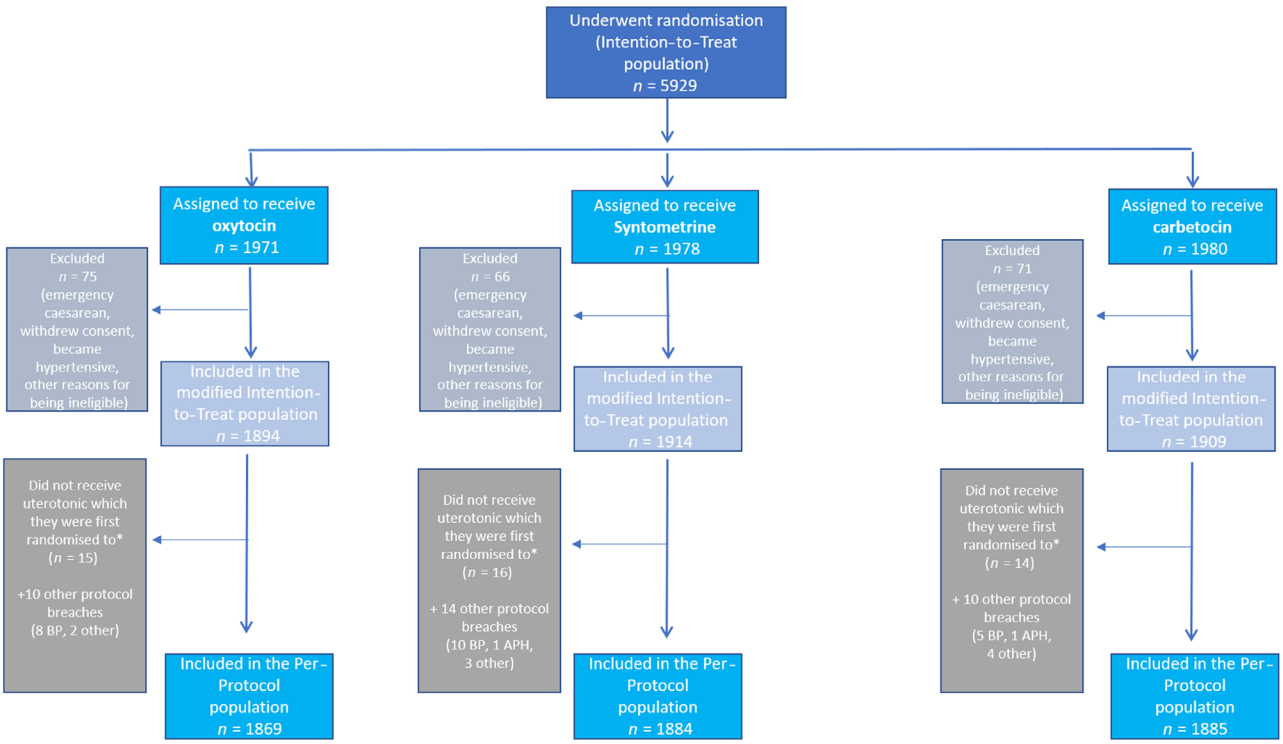

Figure 1. CONSORT diagram showing flow of participants through The IMox Study. *Uterotonic that participants originally randomised to discarded as out of fridge too long (birth believed to be imminent when randomised but took longer). Next consecutively numbered drug administered. APH, antepartum haemorrhage; BP, blood pressure.

Table 1. Baseline characteristics (modified Intention-To-Treat population)

Characteristic	Oxytocin (*n* = 1894)	Syntometrine (*n* = 1914)	Carbetocin (*n* = 1909)
Median age, years (IQR)	30 (26–33)	30 (26–34)	30 (26–34)
Median BMI, kg/m^2 (IQR)	25 (22–30)	25 (22–30)	25 (22–30)
Parity			
Nulliparous, *n* (%)	814 (42.9)	852 (44.6)	780 (40.9)
Parity 1–4, *n* (%)	1061 (56.0)	1032 (54.0)	1095 (57.3)
Parity 5+, *n* (%)	20 (1.1)	25 (1.4)	33 (1.8)
History of previous PPH, *n* (% of parous women)	155 (14.3)	127 (12.0)	147 (13.0)
Median gestational age at birth, completed weeks (IQR)	39 (38–41)	39 (38–40)	40 (38–41)
Onset of labour induced, *n* (%)	1339 (70.7)	1340 (70.3)	1391 (73.1)
Median birthweight (kg) (IQR)	3.43 (3.08–3.77)	3.42 (3.07–3.77)	3.44 (3.11–3.79)
Mode of birth			
Spontaneous, *n* (%)	1492 (78.8)	1453 (76.2)	1486 (78.0)
Instrumental, *n* (%)	401 (21.2)	454 (23.8)	420 (22.0)
Baseline antenatal utility score from EQ-5D	0.81	0.81	0.81
Asian ethnicity, *n* (%)	66 (3.5)	60 (3.2)	66 (3.5)
Intrapartum characteristics (used in Table S4)			
Prolonged labour, *n* (%)	244 (12.9)	256 (13.4)	219 (11.5)
Pyrexia in labour, *n* (%)	66 (3.5)	89 (4.7)	76 (4.0)
Spontaneous birth, *n* (%)	1492 (79.8)	1453 (76.2)	1486 (78.0)

Table 2. Primary and secondary outcomes by arm

Outcome	Oxytocin (*n* = 1894)	Syntometrine (*n* = 1914)	Carbetocin (*n* = 1909)	Missing data for outcome
Primary outcome				
Need for additional uterotonics (mITT population)	368 (19.5%)	298 (15.6%)	364 (19.1%)	8 participants (4 oxytocin, 2 syntometrine 2 carbetocin)
Need for additional uterotonics (PP population)	(*N* = 1869) 359 (19.2%)	(*N* = 1884) 293 (15.6%)	(*N* = 1885) 359 (19.1%)	7 participants (4 oxytocin, 1 syntometrine, 2 carbetocin)
Secondary outcomes (mITT)				
Median blood loss (ml), (IQR)	500 (290–834)	483 (288–820)	500 (298–837)	Data for weighed blood loss was missing for 8 participants (0 oxytocin, 3 syntometrine, 5 carbetocin)
Weighed blood loss ≥500 ml	949 (50.5%)	920 (48.2%)	961 (50.4%)	
Weighed blood loss ≥1000 ml	355 (18.7%)	352 (18.4%)	330 (17.3%)	
Weighed blood loss ≥2000 ml	74 (3.9%)	59 (3.1%)	56 (2.9%)	
Duration of third stage of labour (minutes), (IQR)	10 (7–14)	9 (6–14)	10 (7–14)	
Blood transfusion	58 (3.1%)	51 (2.7%)	54 (2.8%)	4 participants (2 syntometrine, 2 carbetocin)
Manual removal of placenta	43 (2.3%)	49 (2.6%)	57 (3.0%)	4 participants (1 oxytocin, 3 syntometrine, 1 carbetocin)
Other surgical/mechanical ('non-drug') methods to treat PPH[a]	58 (3.1%)	38 (2.0%)	42 (2.2%)	6 participants (1 oxytocin, 2 syntometrine, 3 carbetocin)
Blood pressure: hypertension in first 2 postnatal hours[b]	134 (7.1%)	233 (12.3%)	132 (7.0%)	21 participants (1 oxytocin, 10 syntometrine, 10 carbetocin)
Blood pressure: hypotension in first 2 postnatal hours[c]	47 (2.5%)	30 (1.6%)	31 (1.6%)	
Nausea	169 (8.9%)	458 (24.0%)	153 (8.0%)	Maternal adverse effects not completed for 3 participants (0 oxytocin, 2 syntometrine, 1 carbetocin)
Vomiting[d]	92 (4.9%)	337 (17.6%)	91 (4.8%)	
Headache	26 (1.4%)	65 (3.4%)	28 (1.5%)	
Dizziness	163 (8.6%)	188 (9.8%)	123 (6.4%)	
Abdominal pain	129 (6.8%)	162 (8.5%)	99 (5.2%)	
Answer 'yes' to question 'Have any of the above symptoms affected your ability to bond with and/or care for your baby in these first few hours?'	83 (4.4%)	160 (8.4%)	56 (2.9%)	188 participants (64 oxytocin, 63 syntometrine, 61 carbetocin)
Mean EQ-5D utility score: all returned antenatal questionnaires	0.8107	0.8104	0.8115	638 participants (217 oxytocin, 210 syntometrine, 211 carbetocin)
Mean EQ-5D utility score: all returned day 1 postdelivery questionnaires	0.7553	0.7470	0.7578	359 participants (135 oxytocin, 113 syntometrine, 111 carbetocin)
Mean EQ-5D utility score: all returned day 14 postdelivery questionnaires	0.9031	0.8910	0.8998	783 participants (264 oxytocin, 262 syntometrine, 257 carbetocin)
Mean EQ-5D utility score for participants with a 'complete' EQ-5D data set: day 14 postdelivery[e]	0.9034 (*n* = 1368)	0.8918 (*n* = 1399)	0.8995 (*n* = 1406)	1544 participants did not have a complete EQ-5D dataset (528 oxytocin, 513 syntometrine, 503 carbetocin)

[a]Composite outcome of examination under anaesthetic/intrauterine balloon/uterine compression suture/interventional radiology.
[b]Defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in the first two postnatal hours.
[c]Defined as diastolic blood pressure < 90 mmHg in the first two postnatal hours.
[d]Vomiting in those not already vomiting in labour.
[e]'Complete' defined as those participants who returned EQ-5D questionnaires antenatally, on day 1 and on day 14.

significant difference between oxytocin and carbetocin, and the percentage receiving an additional uterotonic drug was consistently significantly lower in the Syntometrine arm compared with carbetocin or oxytocin.

In the logistic regression model (see Supplementary material, Table S4), women randomised to carbetocin or oxytocin remained significantly more likely to receive additional uterotonic drugs than those randomised to Syntometrine after adjusting for risk factors and recruiting site. As per protocol, multiple imputation using chained equations was performed, but this did not alter any conclusions.

Table 3. Pairwise comparison of study arms

	Carbetocin versus Syntometrine	Syntometrine versus oxytocin	Carbetocin versus oxytocin
Primary outcome (mITT population)	Percentage difference 3.54% 95% CI 1.14–5.93 Bonferroni corrected 98.3% CI 0.06–6.46 OR 1.28, 95% CI 1.08–1.51, $P = 0.004$ (For non-inferiority comparison see text)	Percentage difference −3.90% 95% CI −6.31 to −1.49 Bonferroni corrected 98.3% CI −6.84 to −0.96 OR 0.75, 95% CI 0.65–0.91, $P = 0.002$	Percentage difference −0.36% 95% CI −2.87 to 2.15 Bonferroni corrected 98.3% CI −3.42 to 2.69 OR 0.98, 95% CI 0.83–1.15, $P = 0.78$
Primary outcome (PP population)	Percentage difference 3.51% 95% CI −1.19 to 5.21 Bonferroni corrected 98.3% CI 0.06–6.44 OR 1.28, 95% CI 1.08–1.51, $P = 0.004$	Percentage difference −3.71% 95% CI −6.14 to −1.28 Bonferroni corrected 98.3% CI −6.66 to −0.70 OR 0.77, 95% CI 0.65–0.92, $P = 0.003$	Percentage difference −0.20% 95% CI −2.73 to 2.32 Bonferroni corrected 98.3% CI −3.27 to 2.87 OR 0.99, 95% CI 0.84–1.16, $P = 0.89$
Secondary outcomes			
Weighed blood loss ≥500 ml	$P = 0.16$, OR 1.10, 95% CI 0.96–1.24	$P = 0.25$, OR 0.93, 95% CI 0.82–1.05	$P = 0.80$, OR 1.02, 95% CI 0.90–1.15
Weighed blood loss ≥1000 ml	$P = 0.37$, OR 0.93, 95% CI 0.79–1.09	$P = 0.82$, OR 0.91, 95% CI 0.83–1.16	$P = 0.26$, OR 0.91, 95% CI 0.77–1.07
Weighed blood loss ≥2000 ml	$P = 0.79$, OR 0.95, 95% CI 0.66–1.38	$P = 0.17$, OR 0.78, 95% CI 0.55–1.11	$P = 0.10$, OR 0.75, 95% CI 0.52–1.06
Duration of third stage of labour	$P = 0.573$, Md[a] 0, 95% CI 0, 0	$P = 0.096$, Md[a] 0, 95% CI −1, 0	$P = 0.269$, Md[a] 0, 95% CI −1, 0
Blood transfusion	$P = 0.76$, OR 1.06, 95% CI 0.72–1.57	$P = 0.52$, OR 0.87, 95% CI 0.59–1.27	$P = 0.68$, OR 0.92, 95% CI 0.63–1.35
Manual removal of placenta	$P = 0.43$, OR 1.17, 95% CI 0.79–1.72	$P = 0.36$, OR 1.14, 95% CI 0.75–1.72	$P = 0.17$, OR 1.33, 95% CI 0.89–1.98
Other surgical/mechanical ('non-drug') methods to treat PPH	$P = 0.64$, OR 1.11, 95% CI 0.71–1.72	$P = 0.04$, OR 0.64, 95% CI 0.42–0.97	$P = 0.10$, OR 0.71, 95% CI 0.48–1.06
Hypertension in first two postnatal hours	$P < 0.001$, OR 0.53, 95% CI 0.42–0.66	$P < 0.001$, OR 1.85, 95% CI 1.48–2.32	$P = 0.88$, OR 0.98, 95% CI 0.76–1.26
Hypotension in first two postnatal hours	$P = 0.91$, OR 0.97, 95% CI 0.59–1.60	$P = 0.83$, OR 0.67, 95% CI 0.43–1.06	$P = 0.07$, OR 0.65, 95% CI 0.41 – 1.03
Nausea	$P < 0.001$, OR 0.28, 95% CI 0.23–0.34	$P < 0.001$, OR 3.22, 95% CI 2.67–3.90	$P = 0.32$, OR 0.89, 95% CI 0.71–1.12
Vomiting	$P < 0.001$, OR 0.23, 95% CI 0.18–0.30	$P < 0.001$, OR 4.20, 95% CI 3.30–5.35	$P = 0.91$, OR 0.98, 95% CI 0.73–1.32
Headache	$P < 0.001$, OR 0.42, 95% CI 0.27–0.66	$P < 0.001$, OR 2.53, 95% CI 1.60–4.02	$P = 0.80$, OR 1.07, 95% CI 0.63–1.83
Dizziness	$P < 0.001$, OR 0.63, 95% CI 0.50–0.80	$P = 0.18$, OR 1.16, 95% CI 0.93–1.45	$P = 0.01$, OR 0.73, 95% CI 0.57–0.93
Abdominal pain	$P < 0.001$, OR 0.59, 95% CI 0.46–0.76	$P = 0.05$, OR 1.27, 95% CI 1.00–1.62	$P = 0.04$, OR 0.75, 95% CI 0.57–0.98
Answer 'yes' to question 'Have any of the above symptoms affected your ability to bond with and/or care for your baby in these first few hours?'	$P < 0.001$, OR 0.33, 95% CI 0.24–0.45	$P < 0.001$, OR 2.00, 95% CI 1.52–2.62	$P = 0.02$, OR 0.66, 95% CI 0.47–0.93

[a]Md = difference of medians (continuous data).

Secondary outcomes and adverse effects

There is no evidence of differences in the distribution of blood loss volume (≥500 ml, ≥1000 ml, ≥2000 ml) between all arms or any pairwise comparisons (Table 3). Duration of the third stage of labour and rates of blood transfusion were not different between groups, and mean transfusion rate was 2.9% (see Supplementary material, Table S5 for additional transfusion data).

Group allocation did not affect the rate of manual removal of placenta, but use of Syntometrine did significantly reduce the rate of 'non-drug' PPH treatment methods, but only when compared with oxytocin (2.0% versus 3.1%, OR 0.64, 95% CI 0.42–0.97).

Carbetocin and oxytocin were associated with less hypertension in the first two postnatal hours than Syntometrine (carbetocin versus Syntometrine OR 0.53, 95% CI 0.42–0.66; Syntometrine versus oxytocin OR 1.85, 95% CI 1.48–2.32).

Randomisation had no effect on hypotension rates (Tables 2 and 3). Maternally reported adverse effects differed between groups (Table 2). Nausea, vomiting, abdominal pain and headache were less commonly associated with carbetocin and oxytocin than Syntometrine. Syntometrine and oxytocin caused more dizziness and abdominal pain than carbetocin.

Participants receiving carbetocin or oxytocin were less likely to report a reduced ability to bond with or care for their baby in the first two postnatal hours than those receiving Syntometrine (OR 0.33, 95% CI 0.24–0.45 for carbetocin versus Syntometrine, and OR 2.00, 95% CI 1.52–2.62 for Syntometrine versus oxytocin).

Health-related quality of life

EQ-5D-5L questionnaire responses were available from 5079 (89%) participants antenatally, 5358 (94%) on day 1 postdelivery and 4923 (86%) on day 14 postdelivery. A total of 4173 participants (73%) completed the questionnaire at all three time-points. Mean utility scores were no different between groups at all time-points; utility scores fell at day 1 compared with baseline scores and improved above antenatal scores by day 14. Scores at 14 days for all available data and for patients who completed the EQ-5D at all three time-points were similar, suggesting any missing data were at random.

Serious adverse events

A PPH ≥2000 ml was reportable as a serious adverse event and accounted for 89% (177/198) of all events. The distribution of the causes of the remaining 21 serious adverse events was not different across arms and was not directly attributable to the study drugs. No maternal deaths occurred, and no hysterectomies were performed.

Discussion

Main findings

Intramuscular carbetocin or oxytocin resulted in more additional uterotonic use than IM Syntometrine. Syntometrine reduced the need for non-drug PPH treatments compared with oxytocin. There was no difference in measured blood loss between groups but there were increased maternal adverse effects with Syntometrine compared with both oxytocin and carbetocin. The increase in adverse effects with Syntometrine use explains the reduction in maternally reported ability to bond with and care for her baby in the first 2 hours. Maternal health-related quality of life in the first two postnatal weeks was not different between the uterotonics.

Strengths and limitations

This trial reports the results of the first direct comparison of the three most commonly employed IM uterotonics for prevention of PPH at vaginal birth. The large size, multicentre involvement and broad eligibility criteria of this study support its external validity. The involvement of a Maternity Service User Panel strengthened development of the study protocol. This trial provides data for future analyses of the cost-effectiveness of these agents, which is a WHO priority.[4] The 89–95% response rate for EQ-5D-5L questionnaires was high.

Women with known or suspected hypertensive disorders were excluded from this study, which may limit the generalisability of our results to whole populations. There was a relatively high proportion of participants whose labour was induced because our study was hospital-based; women attending hospital for antenatal assessment are more likely to be induced,[19] and those who are in hospital or undergoing induction are more easily approached for participation. At 71.4%, the proportion of women with an induced labour was higher than the background UK rate (32.6%).[20] Regression analysis (see Supplementary material, Table S4) did demonstrate a positive association between induction of labour and both PPH ≥500 ml (OR 1.22, $P = 0.002$) and the use of additional uterotonics (OR 1.40, $P = 0.002$). A core outcome set for studies evaluating interventions for preventing PPH was published after our study had completed.[11] Three of ten outcomes (shock, transfer for higher level of care and breastfeeding) have not been reported in our study.

Interpretation

The PPH event rate in our study is higher than reported in other recent studies.[5,7,8] PPH ≥500 ml was approximately three-fold higher than in the CHAMPION study[7] and two-fold higher than in the intramuscular oxytocin arm of a recent randomised trial in Dublin.[8] This is unlikely to be a

result of differences in the timing of administration because timing of cord clamping does not increase PPH risk.[21] The high rate of induced labours in our study may be contributing, because induction is associated with increased rates of PPH;[22] the induction of labour rate was lower in both the CHAMPION study (~14%)[7] and the Dublin study (53.1%).[8] Further to this, the rate of instrumental vaginal births in our study was ~21–24%, compared with ~4% in CHAMPION. Instrumental vaginal birth is an important risk factor for PPH,[23] and complex births may be underrepresented in trials used to estimate PPH incidence.[24]

There is insufficient evidence to support one method of blood loss estimation over another,[25] including acceptability to women. We made efforts to exclude liquor and combined volumetric and gravimetric measurement of blood loss by using direct collection of blood along with weighing blood-soaked swabs and linen, excluding dry weights. It is possible that our weighed blood loss might be increased by inadvertent liquor contamination. It is also possible that previously accepted incidence of 5–10% may underestimate the true burden of PPH, particularly now that weighed estimation is more common in routine clinical practice; the incidence of PPH ≥500 ml for all maternities in Wales in 2017 was 34.0%,[26] and was 57.7% after vaginal birth in one Chinese centre in 2018.[27]

There could have been under-reporting in other studies: despite a three-fold difference in PPH rate between this study and CHAMPION,[7] the rate of blood transfusion in IMox was only twice that of the CHAMPION study (mean 2.9% versus 1.45%). The reported transfusion rate in the CHAMPION study is the same as the reported blood loss >1000 ml. Prevalent antenatal anaemia in developing countries may go some way to account for this. The transfusion rate in this study is similar to a previous randomised trial of carbetocin versus oxytocin at caesarean section in the same healthcare region, published in 2010.[28]

The recent CHAMPION Study[7] also did not identify any significant difference between carbetocin and oxytocin for use of additional uterotonics or maternal adverse effects. The CHAMPION Study concluded that there was non-inferiority of carbetocin for PPH ≥500 ml at a margin of 1.16, but there was no significant difference for PPH ≥1000 ml.

Our study results corroborate those of the Cochrane network meta-analysis[29] that concluded Syntometrine use does not reduce PPH ≥1000 ml compared with oxytocin and there are higher rates of adverse outcomes. Our study also corroborates the network meta-analysis findings that Syntometrine may reduce the use of additional uterotonics, although the certainty of the evidence in the network meta-analysis was low.[9] However, our data do not support the network meta-analysis conclusions that Syntometrine and carbetocin probably reduce PPH ≥500 ml compared with oxytocin. Mode of administration may be more important than previously thought. Standard UK practice for vaginal birth is IM administration, but the Dublin study identified that there was a significant benefit to intravenous administration of oxytocin.[8] The pharmacokinetics of carbetocin demonstrate higher peak levels after intravenous administration compared with intramuscular,[30] which may account for the benefits of intravenous carbetocin identified at caesarean section.[31] More research is required to investigate routes of uterotonic administration as well as parallel work to develop tools to prospectively identify women who would benefit from intravenous administration. Finally, we will use our data to investigate the cost-effectiveness of the uterotonics employed in this study.

Conclusion

This large multicentre randomised controlled trial demonstrated that the use of IM Syntometrine during the third stage of labour reduced the use of additional uterotonic agents compared with both IM oxytocin and carbetocin, and reduced the use of non-drug PPH treatments compared with oxytocin. However, PPH and transfusion rates were not different between the assigned uterotonics. Syntometrine use resulted in more frequent maternal adverse effects and compromised a mother's ability to bond with and care for her baby. There were no differences in day 1 and day 14 quality of life scores between the three uterotonics.

Our findings inform choices for prevention of PPH at vaginal birth for clinicians, policy-makers and women. The adverse effects of Syntometrine are an important disadvantage in terms of safety and maternal birth experience and must be weighed up against the benefit of reduced requirement for additional uterotonics. Moreover, Syntometrine requires secure cold-chain storage and it is not widely available or used in many settings globally.[32]

Oxytocin and carbetocin appear to be equally acceptable to women and efficacious when used intramuscularly. Our data support the WHO recommendation that both oxytocin and carbetocin are appropriate drugs for PPH prevention where their costs are comparable.

Disclosure of interests

TJD has been a paid speaker for Ferring Pharmaceuticals. There are no other conflicts of interests. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

HvdN, TD, DS and CW designed the study. ND and EM advised on the statistical analysis of the study. HvdN, SB, MM, MA, JK, CW, CB, SOB and TD conducted the study.

HvdN, ND, EM and TD analysed the data. HvdN wrote the paper and prepared the figures and tables. All the authors revised the paper and agreed to the submission of the final version of the manuscript. The authors vouch for the accuracy and completeness of the data and analyses, and for the fidelity of this report.

Details of ethics approval

This trial was approved by the South Central – Oxford B Research Ethics Committee, United Kingdom, on 28 October 2014 (reference 14/SC/1312).

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The costs for the trial medications and blinding were covered by Ferring Pharmaceuticals, with no further trial input. This funder had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit the publication. A small grant from North Bristol NHS Trust paid for some equipment and training costs. This study was included in the National Institute for Health Research Clinical Research Network Portfolio. Staffing costs were internally covered by Research and Innovation departments at participating sites.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

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

Figure S1. Supplement illustrating drug blinding.

Figure S2. Interpretation of non-inferiority comparison Carbetocin versus Syntometrine (adapted from Schumi and Wittes, *Trials* 2011;12:106).

Table S1. Baseline characteristics for the per-protocol (PP) population.

Table S2. Primary and secondary outcomes for per-protocol (PP) population.

Table S3. Pairwise comparison (OR, 95% CI) for the per protocol population.

Table S4. Logistic regression model relating to need for additional uterotonic drugs, and postpartum haemorrhage ≥500 ml for per protocol population.

Table S5. Additional transfusion data for modified intention-to-treat and per-protocol populations. ■

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