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ORIGINAL ARTICLE

# Carbetocin reduces the need for additional uterotonics in elective caesarean delivery: a systematic review, meta-analysis and trial sequential analysis of randomised controlled trials

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**ABSTRACT**

**Background:** Carbetocin has been found to be superior to oxytocin in terms of need for additional uterotonics and prevention of postpartum haemorrhage at caesarean delivery. However, this is based on combined data from labouring and non-labouring parturients and it remains unclear how effective carbetocin is in the purely elective setting. The aim of this review was to compare carbetocin to oxytocin in elective caesarean delivery.

**Methods:** Medline, Embase, CINAHL, Web of Science, and the Cochrane databases were searched for randomised controlled trials in any language. The primary outcome was need for additional uterotonics. Secondary outcomes were mean blood loss, need for blood transfusion and incidence of postpartum haemorrhage >1000 mL.

**Results:** Nine studies with a total of 1962 patients were included. Trial sequential analysis confirmed that the information size (n=1692) had surpassed that required (n=1166) in order to demonstrate a statistically significant reduction in the use of additional uterotonics. Need for additional uterotonics was reduced by 53% with carbetocin compared to oxytocin (OR 0.47, 95% CI 0.34 to 0.64; $P$ <0.001, $I^2$=63.5). The number needed-to-treat was 11. The risk of bias, data heterogeneity and inconsistency in reporting bleeding outcomes made it difficult to reach definite conclusions about prevention of PPH.

**Conclusions:** Carbetocin is associated with a reduced need for additional uterotonics when compared with oxytocin at elective caesarean delivery. Standardisation of bleeding-related outcomes in studies is necessary to facilitate synthesis of data in future analyses.
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***Keywords***: Carbetocin; Elective caesarean; Postpartum haemorrhage; Trial sequential analysis

## Introduction

Primary postpartum haemorrhage (PPH) is a major cause of morbidity and the leading cause of direct maternal death worldwide,[1] with uterine atony accounting for approximately 70% of cases.[2] Oxytocin is the most commonly used uterotonic in the developed world, with recent Cochrane reviews showing that it is effective for treating PPH.[3,4] However, failure of PPH prophylaxis with oxytocin, as shown by the need for a rescue uterotonic, has been demonstrated to be as high as 13% in women having an elective caesarean delivery (CD).[5] According to NHS statistics, 12–13% of all deliveries were by elective CD in England in 2017 and 2018 (NHS Digital, Hospital Episode Statistics for England, HES and Maternity Statistics).

Carbetocin, a synthetic analogue of oxytocin, has an elimination half-life of 40 minutes compared with 10 minutes for oxytocin, such that it can be administered as a single dose without need for a continuous infusion.[6] After intramuscular administration, the onset of uterine activity onset is less than two minutes and its bioavailability is 80%.[6] Studies comparing carbetocin with oxytocin in CD suggest carbetocin is superior in terms of blood loss and need for additional uterotonics.[7–9] However, evidence of its superiority in reducing the incidence of PPH has been variably reported in systematic reviews.[10–12] Furthermore, these reviews have included studies with mixed populations of both emergency and elective CDs, at which the former population have a higher risk of PPH and an increase in the heterogeneity of estimates of bleeding outcomes. The reviews also

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made no adjustment of significance levels to take into account repetitive testing with accumulating data.

The results of traditional meta-analyses have been questioned due to the increased risk of type I (false positive) and type II (false negative) errors when participant and trial numbers are inadequate, when repeated hypothesis testing increases type I errors, and because of the potential for increased heterogeneity when trial numbers are higher.[13,14] It is unclear whether there is a statistically significant advantage of carbetocin in elective CD with respect to clinically important outcomes or whether such an advantage might justify the increased cost compared with current methods of prophylaxis. Trial sequential analysis (TSA) has been shown to prevent false positive results when data are sparse, or prior negative or equivocal results are updated,[15,16] and may also prevent false negatives.[13] This method uses alpha spending functions to take into account the repetitive hypothesis testing inherent when new data are added each time the analyses are updated. A focused review on elective CD incorporating TSA would provide evidence for the use of carbetocin; specifically, whether there is enough information to provide definitive evidence regarding its superiority over oxytocin at elective CD.

The objective of this review was to determine, using TSA, the clinical effectiveness of carbetocin compared with oxytocin in the setting of elective CD. A preliminary search of the literature to explore relevant outcomes demonstrated inconsistent reporting of bleeding-related outcomes in trials comparing uterotonics at CD. Treatment failure, as shown by the need for a further therapeutic dose of uterotonic, is a commonly used surrogate for the efficacy of PPH prophylaxis.

## Methods

This study was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[17] and the protocol registered on PROSPERO (CRD42017074859, http://www.crd.york.ac.uk/PROSPERO).

### Search strategy

A peer-reviewed literature search was undertaken using Medline, Embase, CINAHL, Web of Science, and the Cochrane database. The search included all studies published in any language from the start of the databases to 14 February 2019. Search terms including and relating to the following key words and medical subject heading (MeSH) terminologies were used: carbetocin, uterotonics, postpartum haemorrhage, caesarean. An outline of the search strategy is presented in the supporting information (Table S1). Hand searching of full text reference lists as a secondary search was undertaken. Records were managed using a reference management tool (Mendeley Desktop Version 1.17.9 ©2008–2016 Mendeley Ltd.).

### Selection criteria

Randomised controlled trials comparing the use of carbetocin with oxytocin in elective CD were eligible for inclusion. Studies were excluded if they did not compare carbetocin to oxytocin or if they focused on carbetocin use in emergency CD or vaginal delivery populations. Systematic reviews, conference abstracts and letters were also excluded. The primary outcome was the need for additional uterotonics whilst secondary outcomes were mean blood loss, need for blood transfusion and incidence of PPH (>1000 mL).

### Data extraction

The search was conducted by a single investigator (DO). All papers selected as potentially eligible for inclusion were reviewed and the data extracted independently by two investigators (DO and JVR) using a predesigned data extraction tool in Microsoft Excel 2016 (Microsoft Corp, Redmond, WA). Any disagreements were resolved through discussion or arbitration by a third investigator (DM). Extracted data included geographical location, delivery mode, cohort size, interventions, and primary and secondary outcome measures. Statistical results (relative risks, *P*-values, confidence intervals (CI)) were extracted and reported if provided in the manuscript. Authors were contacted for further information if there were inadequate data for analysis or specifically for data on elective CD rather than a mixture of urgencies or delivery modes.

### Statistical analysis

The main findings and recommendations of each study were summarised in tabular format. The statistical analysis of the pooled data was performed using Comprehensive Meta-Analysis, Version 3.0 (Biostat Inc, USA). Meta-analysis was performed using random effects modelling. The $I^2$ statistic was used to quantify the heterogeneity between the trials. Values of $I^2$ <40% were considered nonsignificant, 40–60% were considered to represent moderate heterogeneity and values higher than 60% were reported as high heterogeneity. For frequency variables, the pooled results were reported as Mantel-Haenszel odds ratios (MH OR) along with their 95% CI. For continuous variables, results were expressed as pooled means or pooled mean difference with 95% CI. For mean blood loss, values expressed in terms of median and interquartile range in those trials where no individual data could be obtained after contacting the authors, the mean and standard deviation were estimated for pooling using Hozo's method.[18] In a few trials, although the mean blood loss was reported, the associated variance was not available. In the absence of raw data, we imputed these missing variances as per

Cochrane collaboration recommendations. We used the mean variance, which was calculated from the other available variances of the included studies.[19,20] A value of $P<0.05$ was considered statistically significant for pooled results of the above variables.

To determine whether the cumulative sample size was appropriately powered for the obtained pooled effect values and to avoid random error, we performed TSA using the TSA Module 2017 (Copenhagen Trial Unit, Denmark). Both conventional (with alpha of 5%) and trial sequential monitoring boundaries (for random effects modelling with alpha of 5%, beta of 15%) were constructed for the need for additional uterotonics as a binary outcome variable. The heterogeneity correction in the TSA was set to variance-based and the random effects model was applied. A cumulative, sequential Z-score curve was constructed and used to evaluate adequacy of the present evidence. The required information size (IS), that denotes the number of patients, was defined and calculated using the above modelling, as the number of participants and events necessary to detect or reject an a priori assumed intervention effect in the meta-analysis.

### Risk of bias assessment

Criteria used to assess the risk of bias were based on the recommendations of the Cochrane Collaboration[21] and included: method of randomisation; concealed treatment allocation; blinding during pre-, peri- and postoperative care; blinded data collection and analysis; blinded adjudication of study endpoints; and completeness of data. Two authors (DO and PMS) undertook the risk of bias assessment and consensus was reached through arbitration with a third author (DM). Other forms of bias were also considered, such as study power, selection bias prior to randomisation, poor generalisability, subjective means of assessing blood loss or competing interests. The graphical synopsis of the assessment was constructed using the software Review Manager 5.0 (Cochrane Collaboration, Oxford, UK). The evidence for the outcomes were rated using the GRADE approach, as high, moderate, low or very low.[22] Studies were also assessed for possible publication bias, initially using a funnel plot and subsequently quantified using the Egger's test.

## Results

A total of 1889 articles were identified after removal of duplicates, but the majority were excluded as they were not RCTs. Nineteen full-text articles were assessed for eligibility, with an additional two identified from hand searching (Fig. 1). After exclusions, nine RCTs with a total of 1962 patients were included in the review.[5,6,9,23–28] Table 1 outlines the study characteristics. All the studies included patients undergoing elective CD under regional anaesthesia, except one which investigated elective CD under general anaesthesia.[5] One study originally included a mixture of elective and emergency cases but the author was contacted and provided raw data for the elective cases to be analysed separately.[23] Four studies included patients with risk factors for PPH,[5,9,25,27] with the remainder excluding such patients. The investigative dose of intravenous (IV) carbetocin was 100 μg in all the studies and was compared with a single bolus dose of IV oxytocin 5 IU in three of the studies.[23,24,26] Four studies followed the oxytocin bolus (2.5–10 IU IV) with an infusion of varying strength and duration, as part of the study protocol.[6,9,27,28] Two studies also compared carbetocin with misoprostol, one in combination with oxytocin[25] and one as a separate third intervention.[27] One study used normal saline as a placebo in a third intervention.[26] The need for additional uterotonics was used as the primary outcome measure in five studies,[5,9,23,25,27] the remainder using mean blood loss[6] or haemodynamic indices.[24,26,28] All nine studies considered the need for additional uterotonics as either a primary or secondary outcome. The most frequent secondary outcome measures were estimated blood loss (EBL) and EBL >1000 mL, as a measure of PPH; and the need for blood transfusion.

## Meta-analysis

Pooled results were effectively generated for the variables outlined below.

### Need for additional uterotonics

Values for this variable were reported in all nine trials and included 845 patients in the carbetocin group and 848 patients in the oxytocin group. The incidence of requirement for additional uterotonics was 9.11% (95% CI 7.35 to 11.24) with carbetocin and 18.16% (95% CI 15.17 to 20.90) with oxytocin. Overall, the additional uterotonics requirement was lowered by 53% with the use of carbetocin and the MH OR for this pooled result was 0.47 (95% CI 0.34 to 0.64, $P<0.001$, $I^2$ 63.5%, random effects modelling) (Fig. 2). The number-needed-to-treat (NNT) with carbetocin was 11.05.

To explore the high heterogeneity, we attempted a sensitivity analysis using a single-study-removal method. The study by Fahmy et al.[5] contributed highly towards the heterogeneity. Excluding this study from the analysis dropped the overall heterogeneity to 10.81%. Pooled values with and without this trial are shown in Fig. 2.

With the conventional boundary for a statistical significance of $P=0.05$, an information size in excess of 1021 was required to detect the observed effect size. For constructing the alpha-spending boundary based upon a low risk of bias model, where at least a 58.7% difference between groups in the need for additional

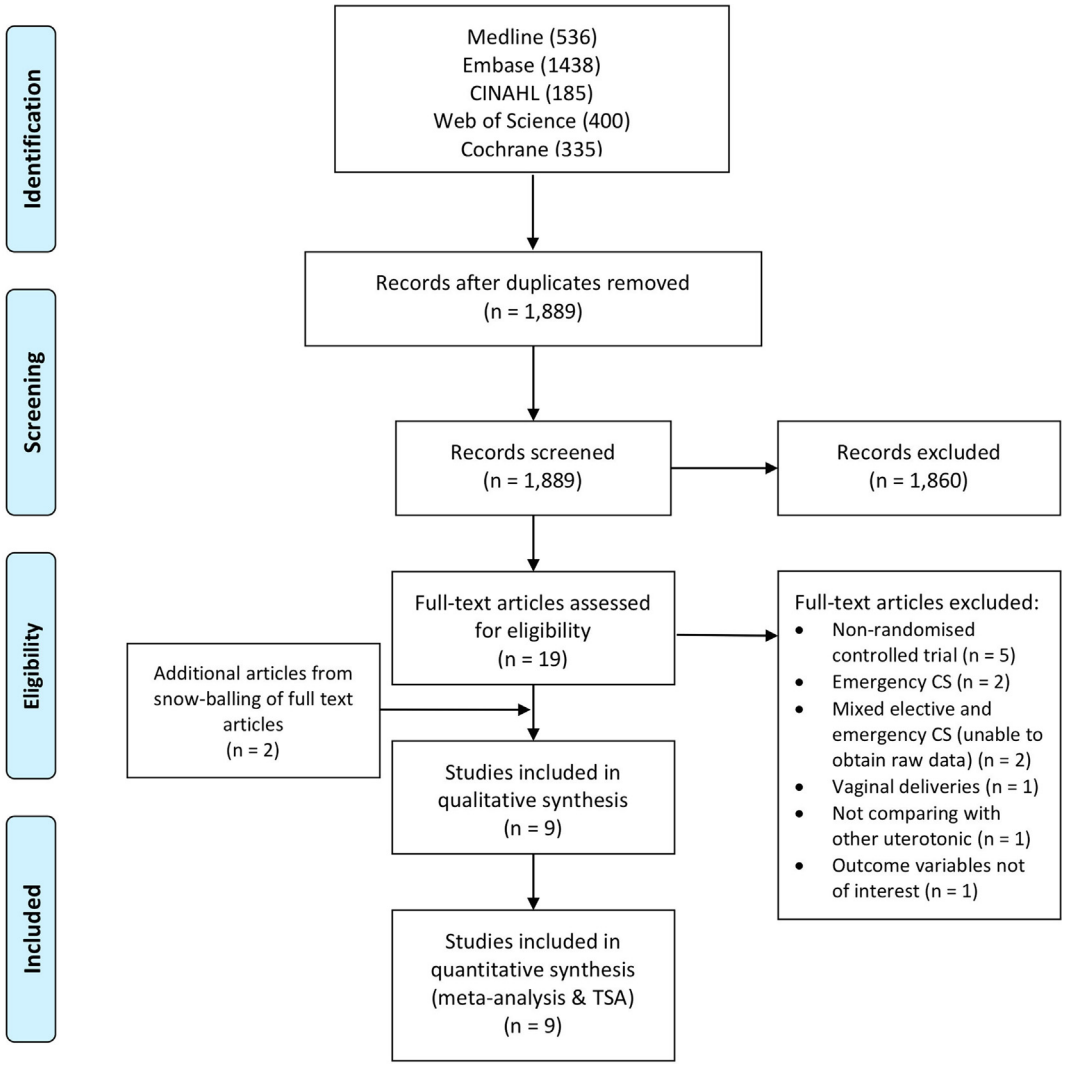


**Fig. 1** PRISMA flowchart of systematic research

uterotonics was demanded, an information size of at least 1166 was required. With 1693 patients, the cumulative Z-score trail of our sequential trials crossed both the conventional and alpha-spending boundary (Fig. 3), meaning that additional trials are unlikely to change the outcome. Even when the study by Fahmy et al.[5] (contributing 60 patients) was excluded from the TSA in the sensitivity analysis, the total information size remained above the new adjusted required value of 1166.

## Mean blood loss

Comparative blood loss was reported as mean or total blood loss or EBL in six trials.[5,23,25–28] Patients receiving carbetocin had less blood loss (mean 478 mL) than those receiving oxytocin (mean 573.5 mL), but these values failed to attain statistical significance ($P$=0.12, Fig. 4). The pooling suffered high heterogeneity of 98.49%, possibly related to the huge variations in the blood loss reported across different trials. To look at heterogeneity, we performed the sensitivity analysis using a single-study-removal method. However, nearly all studies contributed equally towards the high heterogeneity and this did not change significantly on removal of any individual trial.

## Need for blood transfusion and incidence of PPH

Five trials reported the need for blood transfusion[5,23,25–27] and three reported the incidence of PPH (EBL >1000 mL).[23,26,27] However, bleeding outcome data were not uniformly reported across the trials. Consequently, pooling of this data was considered inappropriate and this analysis was not performed.

## Quality

A risk of bias assessment was performed on each of the studies (Supporting information, Fig. S1). One study did not disclose how subjects were randomised or how

**Table 1 Demographics of included studies**

| Author (year) | Location | Cohort size | PPH risk factors present | Type of anaesthesia | Intervention | Primary outcome(s) | Secondary outcomes |
|---|---|---|---|---|---|---|---|
| Attilakos[23] (2010) | UK | 222 | No | RA (unspecified) | – Carbetocin 100 μg IV (n=106)<br>– Oxytocin 5 IU IV (n=116) | Need for additional uterotonics | – EBL<br>– EBL >1000 mL<br>– Need for blood transfusion |
| Boucher[22] (1998) | Canada | 57 | No | Epidural | – Carbetocin 100 μg IV (n=29)<br>– Oxytocin 2.5 IU IV bolus then 30 IU 16-h infusion (n=28) | Mean blood loss | – Need for additional uterotonics |
| Dansereau[8] (1999) | Canada | 635 | Yes | RA (unspecified) | – Carbetocin 100 μg IV (n=317)<br>– Oxytocin 5 IU IV bolus then 20 IU 8-h infusion (n=318) | Need for additional uterotonics in first 48 hours | None mentioned |
| el Sharkwy[25] (2013) | Egypt | 380 | Yes | Spinal | – Carbetocin 100 μg IV (n=190)<br>– Misoprostol 400 μg SL + Oxytocin 20 IU infusion (n=190) | Need for additional uterotonics | – EBL<br>– Need for blood transfusion |
| Elbohoty[27] (2016) | Egypt | 263 | Yes | Spinal | – Carbetocin 100 μg IV (n=88)<br>– Misoprostol 400 μg SL (n=89)<br>– Oxytocin 10 IU IV then 20 IU 4-h infusion (n=86) | Need for additional uterotonics | – Total blood loss<br>– EBL 500–1000 mL<br>– EBL >1000 mL<br>– Need for blood transfusion |
| Fahmy[5] (2016) | Egypt | 60 | Yes | GA | – Carbetocin 100 μg IV (n=30)<br>– Oxytocin 20 IU IV (n=30) | Need for additional uterotonics | – Total blood loss<br>– Need for blood transfusion |
| Mannaerts[28] (2018) | Belgium | 58 | No | CSE | – Carbetocin 100 μg IV (n=32)<br>– Oxytocin 5 IU IV then 10 IU 24-h infusion (n=26) | Nausea, vomiting, haemodynamics | – Need for additional uterotonics<br>– Hb change 48 hours post (substitute for total blood lost and PPH) |
| Moertl[24] (2011) | Germany | 56 | No | Spinal | – Carbetocin 100 μg IV (n=28)<br>– Oxytocin 5 IU IV (n=28) | Haemodynamics | – Need for additional uterotonics |
| Rosseland[26] (2013) | Norway | 76 | No | Spinal | – Carbetocin 100 μg IV (n=25),<br>– Oxytocin 5 IU IV (n=26)<br>– Placebo 5 mL 0.9% saline IV (n=25) | Haemodynamics | – EBL<br>– EBL >1000 mL<br>– Need for additional uterotonics<br>– Need for blood transfusion |

CSE: combined spinal-epidural; EBL: estimated blood loss; GA: general anaesthesia; Hb: haemoglobin; IU: international units.; IV: intravenous; PPH: postpartum haemorrhage; RA: regional anaesthesia; SL: sublingual.

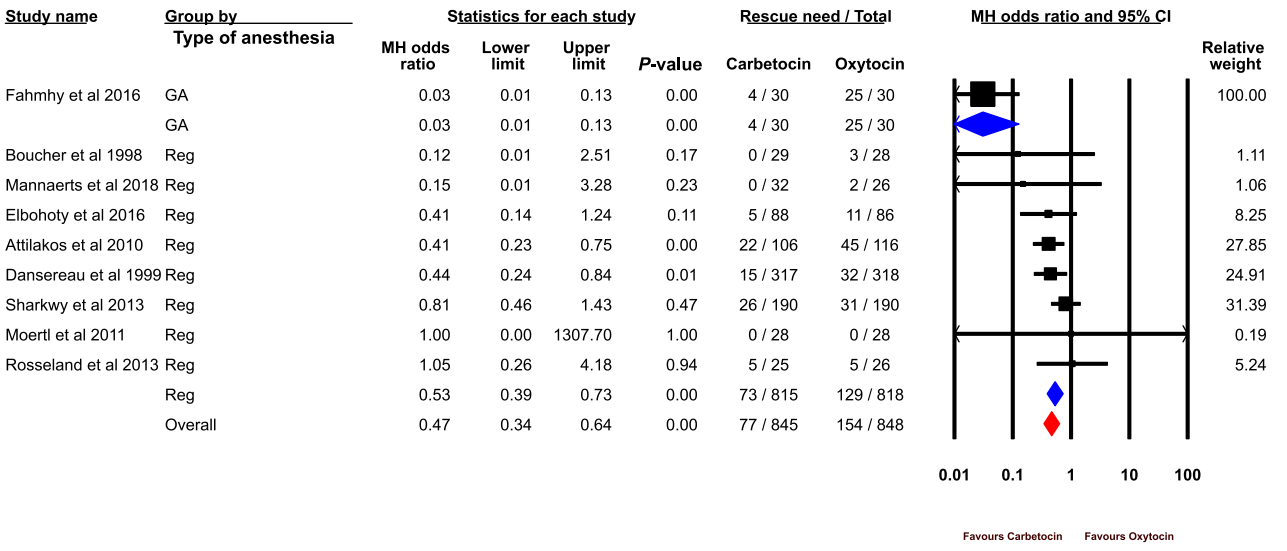


**Fig. 2** Mantel-Haenszel odds ratios (MH OR) for need for additional uterotonics. GA: general anaesthesia. Reg: regional anaesthesia.

allocation was concealed.[6] Two studies used random blocks of two, allowing the possibility of allocations to be guessed and thus introducing bias.[9,25] All studies were blinded to participants and personnel, as was outcome assessment. Two studies explicitly revealed that incomplete and artefactual outcome data led to a high number of participant exclusions from analysis.[23,28] Other forms of bias were unclear in eight of the nine studies, due to: no specified sample size calculations to determine study power; selection bias prior to randomisation; blood loss assessment by haemoglobin estimation;, the counting rather than weighing of swabs or unspecified techniques; and competing interests related to a sponsoring company. The GRADE framework was used to rate the quality of the evidence and is shown in Table 2.

## Publication bias

No significant publication bias was found in the reporting of the primary variable (need for additional uterotonics). The funnel plot (Supporting information, Fig. S2) demonstrated near-symmetrical distribution of trials and an Egger's test showed an X-axis intercept at −0.97 with a *P*-value of 0.372 (two-tailed).

## Discussion

This analysis demonstrates that there is a reduced need for additional uterotonics with carbetocin use at elective CD when compared with oxytocin. This is a more precise estimate than previous analyses,[8,9] most likely reflecting the restriction of clinical context to elective surgery, as well as the addition of data from the 368 patients assessed in the four trials[23–26] published since the most recent of those reviews.[9] The TSA confirms the validity of the result, demonstrating that the alpha-spending boundary was crossed after the second study[9] in this review and that the required information size was reached, so minimising the chance of both type I and II errors. Since the publication of Dansereau et al.'s study[9] there have been a further seven clinical trials recruiting a total of 1115 participants. Although three of those trials (190 participants) were primarily assessing other effects of carbetocin (nausea, vomiting and haemodynamics), the other four all assessed the need for additional uterotonics as the primary outcome. Employment of TSA during the design stage of those studies may have diverted research resources elsewhere.

The meta-analysis of the need for additional uterotonics showed moderate heterogeneity but sensitivity analysis revealed that removal of the Fahmy et al. study[5] reduced this substantially. This is not surprising as the clinical context was different from the other studies. Fahmy et al. recruited women having CD of twins under general anaesthesia with isoflurane. Volatile anaesthetics have a tocolytic effect which could be expected to influence the estimated effect size.

The inclusion of bleeding-related outcomes and the method of their reporting (total blood loss, incidence of PPH >500 mL or >1000 mL, change in haematocrit or need for blood transfusion) was inconsistent between the studies included in our review. Total blood loss was the most common bleeding-related outcome reported. The between-study variation was calculated to be very high. The pooled estimate of the difference

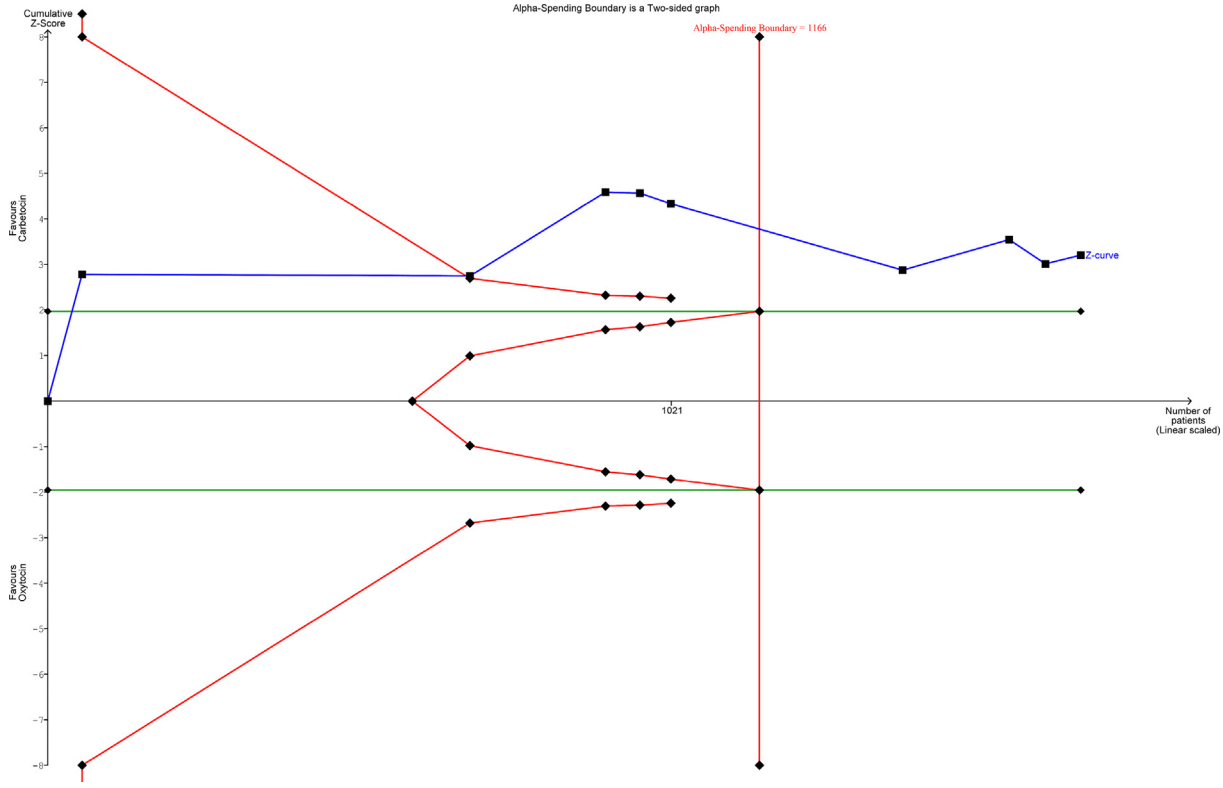


**Fig. 3** Trial sequential analysis (TSA) for incidence of need for additional uterotonics, demonstrating superiority of carbetocin over oxytocin. The lower half of the graph below the zero axis represents the area of advantage with oxytocin and the upper half represents the advantage area with carbetocin. The green lines at +1.96 and −1.96 on the Y-axis represent the conventional model boundaries for TSA with an $\alpha$ of 5%. The minimum required information size (IS) for the conventional boundary model for making conclusion is 1021. Our cumulative z-score line (blue) crosses the conventional boundaries (green lines) indicating superiority of carbetocin over oxytocin is indicated based upon convention model. This is further demonstrated by the alpha-spending model in the graph. The red lines represent the alpha-spending boundary (upper O'Brien Fleming with $\alpha$ of 5%, low risk of bias). The minimum required IS for the alpha-spending boundary model is 1166 (vertical line intersecting X-axis in red). As our cumulative Z-score is well past the minimum IS needed and cumulative Z-scores cross both the conventional and alpha-spending boundaries, superiority of carbetocin over oxytocin is indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article)

between the carbetocin and oxytocin groups was, unsurprisingly, small and both clinically and statistically insignificant. The high heterogeneity was undoubtedly a reflection of the wide variation and subjectivity of the methods used to measure this important clinical outcome. More objective methods of assessing blood loss are urgently needed to compare interventions when the risk of PPH is higher, such as at emergency CD. The CoRe Outcomes in Women's and Newborn health (CROWN) initiative is a consortium of international journals formed to promote the development and reporting of core outcome sets.[29] Recent work by Meher et al.[30] used the Delphi method to reach stakeholder consensus on such an outcome set for the prevention of PPH and nine core outcomes were identified: blood loss; shock; maternal death; use of additional uterotonics; blood transfusion; transfer to a higher level of care; women's sense of well-being, acceptability and satisfaction with the intervention; breastfeeding; and adverse effects. Consistent reporting of these outcomes in future trials would allow a meaningful synthesis of the data, particularly related to bleeding outcomes and adverse effects.

Previous pairwise meta-analyses have not restricted their review question to elective CD. There is good quality evidence demonstrating greater uterotonic dose requirements, for both oxytocin and carbetocin, to achieve adequate uterine tone in labouring women undergoing CD when compared to non-labouring women.[31–33] Examination of the studies included in the Cochrane review[8] reveals that the same dose of carbetocin (100 μg) was used in all studies regardless of the mode of delivery.[10] Oxytocin administration, however, varied greatly in both dose and method of delivery but seldom, if ever, differentiated between the "exposure status" of the participants to exogenous oxytocin. Su et al.[8] found a reduced need for additional therapeutic uterotonic (RR 0.62, 95% CI 0.44 to 0.88) in a carbetocin group compared with an oxytocin group when they pooled the results from four trials of CDs regard-

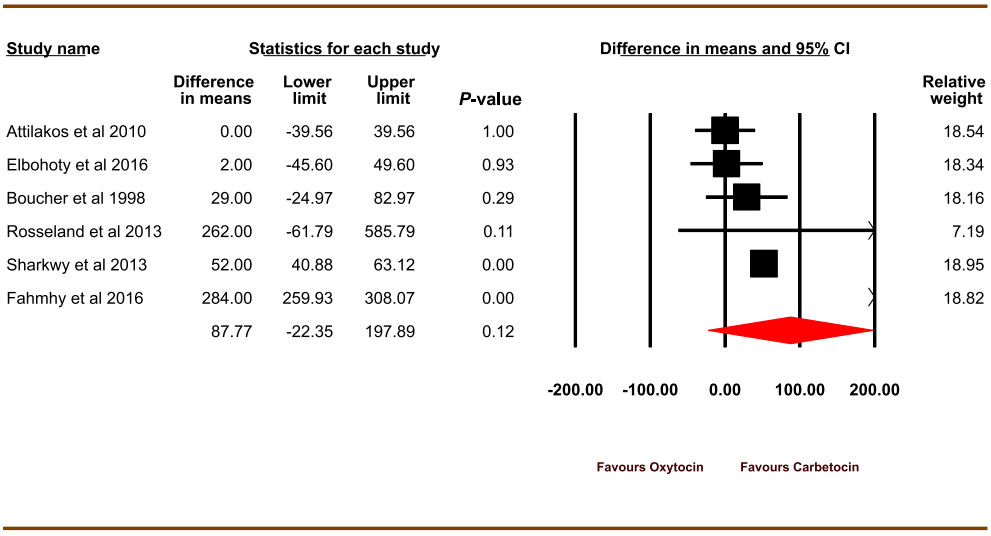


**Fig. 4** Differences in means and 95% confidence intervals (CIs) for mean intraoperative blood loss

**Table 2 GRADE Framework – grades of evidence for each outcome**

Population: Women undergoing elective CD
Settings: Hospitals in Egypt (3 trials), Canada (2 trials), the UK (1 trial), Belgium (1 trial), Germany (1 trial) and Norway (1 trial)
Intervention: Carbetocin
Comparison: Oxytocin

| Outcomes | No. of participants (no. of RCTs) | Relative effect (95% CI) | *P*-value | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|
| Need for additional uterotonics | 1693 (9) | OR 0.47 (0.34 to 0.64)* OR 0.53 (0.39 to 0.73)** | <0.001* <0.001** | ⊕⊕⊕⊕ High | Cumulative Z-score trail crossed conventional and alpha-spending boundaries. Very low heterogeneity ($I^2$=10.8%) after sensitivity analysis with single-study-removal method. |
| Mean blood loss | 1058 (6) | Mean difference 87.77 (−22.35 to 197.89) | 0.12 | ⊕⊕⊖⊖ Low | Downgraded by two levels due to very high heterogeneity among studies ($I^2$=98.49%) |
| Need for blood transfusion | 1001 (6) | – | – | ⊕⊕⊖⊖ Low | Outcome data not uniformly reported. |
| Severe PPH (>1000 mL) | 561 (3) | – | – | ⊕⊖⊖⊖ Very low | Small number of studies. Outcome data not uniformly reported. |

CD: caesarean delivery; OR: odds ratio; PPH: postpartum haemorrhage. *$I^2$=63.5%. **$I^2$=10.8% after single study removal method. GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.;
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

less of the indication or urgency.[10] The small number of trials and the mixed clinical context limits confidence in this result and its applicability to women undergoing elective CD. Jin et al.[11] also found a reduction in uterotonic need (RR 0.68, 95% CI 0.55 to 0.84) in their meta-analysis of CDs including both labouring and non-labouring women.

Any review of the evidence examining carbetocin's ability to prevent PPH is complicated by the variety of comparators employed in different trials. One solution is network meta-analysis which allows evidence from both direct and indirect comparisons to be combined to provide a pooled estimate of effect and rank of competing interventions. A Cochrane review[12] performed such an analysis, to provide multiple comparisons of different uterotonics utilising a multitude of sensitivity analyses, in order to provide a rank order of the various therapeutic options. Carbetocin was ranked ahead of oxytocin with regard to both need for additional uterotonic and incidence of PPH at CD. While the findings do not conflict with those of this analysis, there is good reason to be cautious in comparing the results with those of our study with regard to the internal validity of their analysis in CD and the applicability of their pooled estimates to elective CD. The validity of network meta-analysis is dependent on the assumptions of homogeneity, transitivity and consistency. Whether CD is performed in a labouring or non-labouring parturient influences uterotonic effect, so failing to distinguish between the two casts uncertainty over the validity of the analysis and influences the provision of pooled estimates from which clinicians' decisions about individual patients and cost-effectiveness calculations are informed.

The major strengths of this review are the rigour of the systematic search of the literature and retrieval of unpublished data; the use of TSA to confirm the analysis to be sufficiently powered and the pooled estimates to be statistically significant; and the focus on one clinical context. By focusing on elective CDs, the result from our review is clearer. A repeat of the analysis performed in our study is warranted comparing carbetocin and oxytocin in the population of women requiring intrapartum CD.

Limitations of the review include the low quality of some of the studies included; the fact that only five studies shared the primary outcome of our review; the variability in oxytocin doses used; and the inability to assess important outcomes relevant to bleeding risk and side-effects. One such outcome, PPH, is less common during elective than emergency CD for several reasons but remains an important outcome that we would have preferred to include in our analysis.

This study has demonstrated that further examination of the need for additional uterotonics when using carbetocin at elective CD is unlikely to alter the result of its comparison with oxytocin. Carbetocin is the more expensive of the two options but these results could be used to inform a cost-effectiveness analysis to assess whether the associated saved resources, in terms of additional uterotonics, confer an overall reduction in healthcare costs. An appropriately powered RCT, employing a core set of outcomes to assess the ability of carbetocin to prevent PPH, is now warranted and would assist such calculations.

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## Declaration of interests

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2019.06.007.