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Original Article

Carbetocin versus oxytocin for the prevention of postpartum hemorrhage: A meta-analysis of randomized controlled trials in cesarean deliveries

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ABSTRACT

Objective: Postpartum hemorrhage remains the leading cause of maternal mortality in developing countries and a significant proportion of these cases are attributable to uterine atony. In contrast to the advances made in the treatment of postpartum hemorrhage, there has been few novel prophylactic agents. This study was undertaken to analyze the effectiveness of carbetocin compared to oxytocin for the prevention of postpartum hemorrhage, in the context of cesarean deliveries.

Materials and methods: Major electronic databases were searched for randomized-controlled trials comparing carbetocin with oxytocin. Only trials involving cesarean deliveries were included. Non-randomized trials, non-cesarean deliveries, studies which did not directly compare carbetocin to oxytocin and studies which did not analyze the intended outcomes were excluded. Outcomes analysed were postpartum hemorrhage, additional use of uterotonic and transfusion requirement.

Results: Seven studies involving 2012 patients were included in the meta-analysis. There was a significant reduction in the rates of postpartum hemorrhage (RR 0.79; 95% CI 0.66 to 0.94; $p = 0.009$), use of additional uterotonics (RR 0.57; 95% CI 0.49 to 0.65; $p < 0.001$) and transfusion (RR 0.31; 95% CI 0.15 to 0.64; $p = 0.002$) when carbetocin rather than oxytocin was used. There was significant heterogeneity across studies however, for the outcome of additional uterotonic usage.

Conclusion: Carbetocin is effective in reducing the use of additional uterotonics, reduction in postpartum hemorrhage and transfusion when used during cesarean deliveries. However, despite the potential benefits illustrated in this meta-analysis, the disparity between the cost of carbetocin and oxytocin suggests that locoregional cost-effectiveness analysis should be performed before any decision is made to adopt it for routine prophylaxis.

Introduction

Despite the technological advancement made in the past few decades, postpartum hemorrhage (PPH) remains one of the principal causes of maternal deaths in developing nations [1]. Of late, pharmacologic measures such as anti-fibrinolytic agents, carboprost and recombinant factor VIIa have been added to the obstetricians' arsenal [2]. On the other hand, mechanical measures such as non-pneumatic anti-shock garments, intrauterine balloon tamponade, vacuum-induced uterine tamponade and interventional radiological procedures have surfaced as alternatives to bimanual or aortic compression when PPH occurs [3,4].

While the strides made in treatment of PPH is inspiring, novel prophylactic measures have not made similar progress. Active management of the third stage of labour was previously thought to be a useful strategy to reduce the incidence of PPH but several components of this care bundle such as controlled cord traction and early cord clamping are increasingly under scrutiny, as reflected by recommendations in recent guidelines [5]. Contrary to this, the use of uterotonics at the delivery of the fetal anterior shoulder remains one component of the active management of the third stage which has proven to be consistently beneficial. In fact, a Cochrane review

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involving more than 4200 hundred patients comparing prophylactic uterotonics to placebo and showed that PPH events were halved, underlying its importance [6].

One prophylactic drug which has been introduced in recent times is carbetocin, a synthetic long-acting oxytocin analogue. It has a longer half life of 41 min, allowing it to stimulate a prolonged uterine response of up to an hour after a single intravenous dose, obviating the need for infusion [7]. Currently, carbetocin is only licensed to be used as a prophylaxis rather than for therapeutic indications and in the context of cesarean sections. A Cochrane review in 2012 aptly surmised the evidence for carbetocin in the prevention of PPH but several additional papers have since been published [8–11]. As part of a planned economical analysis for implementation of carbetocin usage in our unit, we performed a limited meta-analysis to determine whether there was any difference in primary outcomes of postpartum hemorrhage, additional uterotonic use (retreatment) and transfusion.

Materials and methods

Literature search

Electronic databases videlicet Medline, Database of Abstract of Reviews of Effects (DARE), Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic reviews and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched without applying any language restrictions from inception until 15th May 2016. The literature search strategy used the keyword “carbetocin”, “oxytocin”, “oxytocin agonist”, “uterotonic” without filters before a combination of “carbetocin” AND “cesarean section” and “carbetocin’ AND “postpartum hemorrhage” were searched (Appendix 1). Publications were cross-checked and duplicates were removed. Titles and abstracts of all articles were examined, followed by scrutiny of the full article when considered potentially relevant. The reference list of the articles were also screened to identify relevant publications. This step and subsequent stages were performed independently by both VHY and HNS.

Study selection and data extraction

The studies considered for inclusion fulfilled the following eligibility criteria: Randomized controlled trial design, comparison was between carbetocin and oxytocin without any restriction to the dose or method of administration. Only trials involving pregnant women undergoing cesarean section were included. Case-controlled studies, retrospective design, those involving vaginal deliveries and comparison between carbetocin and other uterotonics such as ergometrine were excluded. Any disagreement between authors were resolved by consensus and in the event that it failed, the third author was involved in arbitration before finalizing the decision.

Relevant data were extracted and transferred onto a standardized, pre-piloted proforma by the first two authors independently. The author's first name, year of publication, country of origin, number of cases on each arm, incidence of retreatment with additional uterotonics, postpartum hemorrhage and transfusion were extracted. There original authors were not contacted.

Study quality assessment and statistical analysis

The quality of each included study was assessed by VHY and HNS based on several domains, modified from the Cochrane Collaboration's tool for assessing risk of bias [12]. Selection bias, blinding, attrition bias and selective reporting bias for individual studies were tabulated. The risk of bias were classified as low risk, high risk or unclear. Meta-analysis was performed by MAB using the STATA software system (version 11.0; Stata Corporation, College Station, TX, USA). Pooled risk ratios and 95% confidence intervals were obtained by using fixed-effects model [13]. I^2 statistic was used to quantify heterogeneity between studies (I^2 < 25%, no heterogeneity; I^2 25–50%, moderate heterogeneity; and I^2 > 50%, extreme heterogeneity).

Results

We identified seven randomized controlled trials, involving 2012 patients, which met the criteria for inclusion [9–11,14–17]. The process of identifying the studies are shown in Fig. 1. Two of the earliest trials involved elective caesarean sections, another two involving a mixture of elective and emergency cases while three of the later studies involved only emergency caesarean sections. The dose and mode of administration of carbetocin was standardized across all seven studies, whereby 100 μg was given intravenously but doses of oxytocin used were more variable. Five of the seven studies excluded women considered to be at the “highest risk” of postpartum hemorrhage, i.e placenta previa. One of the studies did not specify the exclusion of such cases while in another, 2% of the patients included had placenta previa as the indication of cesarean section [11,16]. Decision for additional uterotonic use was largely based on the surgeon's discretion rather than a prespecified criteria or threshold. Only two of the studies gave more details about the criteria affecting decision for additional uterotonic use in their centre [9,10]. All seven studies reported postpartum hemorrhage and additional uterotonic use as outcomes while only four of the seven studies reported on the need for blood transfusion [9–11,17]. Details of the individual studies are shown in Table 1.

Quality assessment of included studies

All the studies included were randomized. Computer-generated numbers were used in five of the studies but was not described in the other two [14,16]. Block randomization was performed in three of the seven studies in blocks of two, four and ten [9,15,17]. There was low risk of bias in allocation concealment in four of the seven studies [9–11,17], although there was no description in another two of the papers [14,16]. One study which had block randomization in blocks of two and stratified by centre was adjudged to be at high risk of bias [15]. Overall, there was low risk of performance and detection bias, although this risk was unclear in one study [16]. Attrition bias was variable across the studies. Three out of 60 patients were excluded from analysis in one paper [14] because women did not receive the study medication. 59 out of 694 were excluded from analysis in another paper [15] for various reasons due to major protocol violations. However, it was explicitly stated that women who were excluded were done so before blinding was unmasked. 53 out of 600 women were excluded from analysis in a third paper. Reasons for each exclusion were explained and they were similar in both arms [9]. Two of the trials were supported by a research grant from the manufacturer of carbetocin [14,15], while a substantial amount of the study drug were supplied by the manufacturer in another [9]. In one study, the at least two of the authors involved had received travelling expenses from the manufacturer [17]. Details of the above are provided in Appendix 2.

Effects of intervention

The incidence of the three main outcomes we were interested in was summarized in Table 2.

Data on PPH was available from all seven studies included. PPH was defined as bleeding exceeding 1000 mls in 5 studies, more than

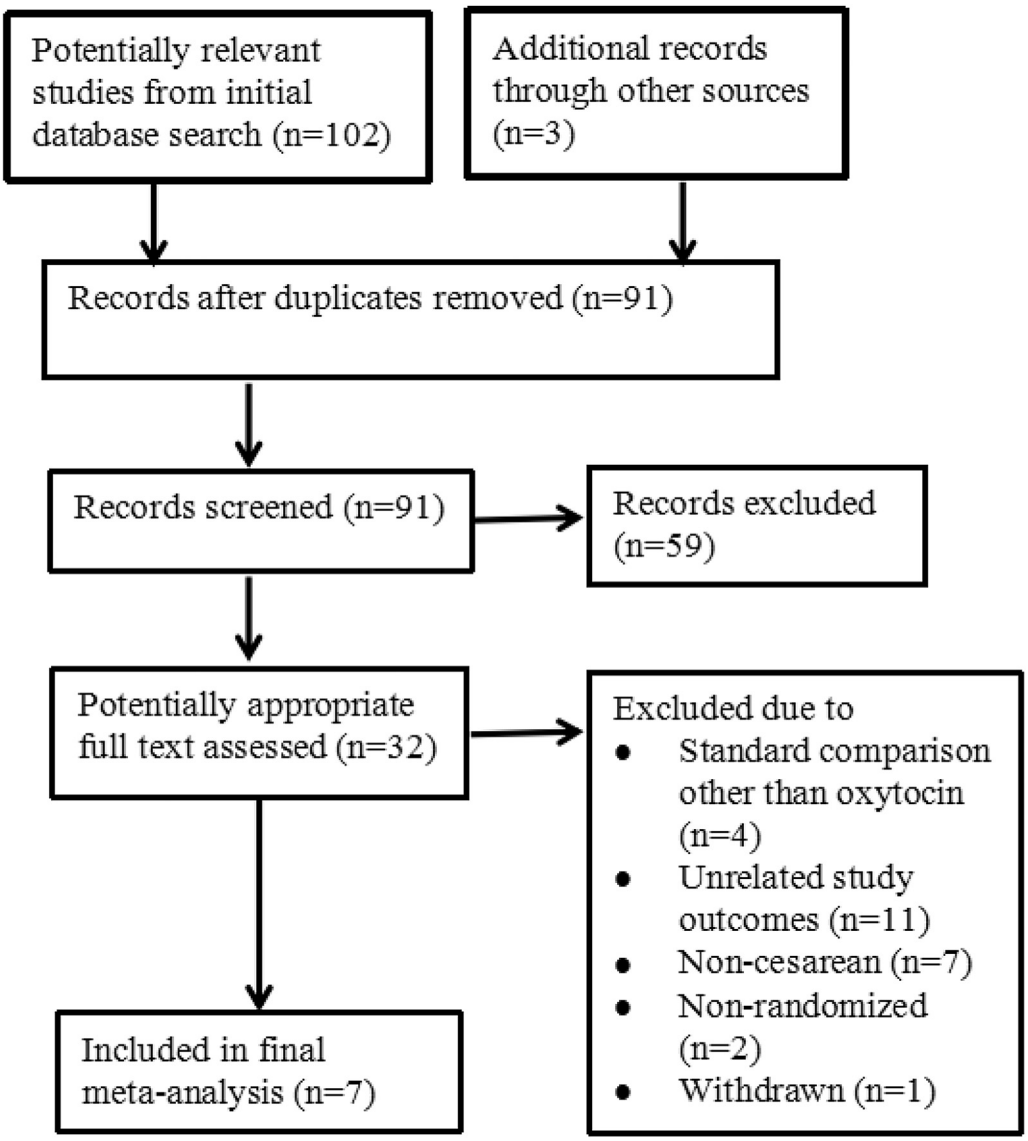

Fig. 1. Flow chart of included studies.

Table 1
Summary of studies included in analysis.

Author (Reference)	Year	Country	Carbetocin (patients)	Oxytocin (patients)	Total (patients)	Comments
Boucher et al.	1998	Canada Single center	29	28	57	Elective
Dansereau et al.	1999	Canada Multicenter	317	318	635	Elective. Excluded previa and abruption
Borruto et al.	2009	Italy Unspecified	52	52	104	Elective & Emergency. Women had at least 1 risk factor for PPH
Attilakos et al.	2010	United Kingdom Single center	188	189	377	Elective & Emergency 25% of women had at least 1 risk factor for PPH
Razali et al.	2016	Malaysia Single center	276	271	547	Emergency. 50% of women had at least 1 risk factor for PPH
El Behery et al.	2016	Egypt Two centres	90	90	180	Emergency. Obese, nulliparous women only
Whigham et al.	2016	Australia Single center	59	53	112	Emergency. Excluded multiple pregnancy. More than half had cesarean in active labour

Table 2
Effects of intervention.

Author	Postpartum hemorrhage		Additional uterotonic		Transfusion	
	Carbetocin (%)	Oxytocin (%)	Carbetocin (%)	Oxytocin (%)	Carbetocin (%)	Oxytocin (%)
Boucher et al.	0/29 (0.00)	1/28 (3.45)	0/29 (0.00)	3/28 (10.71)	–	–
Dansereau et al.	2/317 (0.63)	2/318 (0.63)	15/317 (4.73)	32/318 (10.06)	–	–
Borruto et al.	12/52 (23.08)	23/52 (44.23)	2/52 (3.85)	5/52 (9.61)	–	–
Attilakos et al.	9/188 (4.79)	9/189 (4.76)	63/188 (33.51)	86/189 (45.50)	2/188 (1.06)	5/189 (2.64)
Razali et al.	107/276 (38.77)	120/271 (44.28)	107/276 (38.77)	155/271 (57.20)	6/267 (2.25)	10/271 (3.69)
El Behery et al.	2/90 (2.22)	2/90 (2.22)	2/90 (2.22)	64/90 (71.11)	0/90 (0.00)	14/90 (15.56)
Whigham et al.	13/59 (22.03)	13/53 (24.52)	13/59 (22.03)	7/53 (13.21)	1/59 (1.69)	1/53 (1.89)
Total	145/1011 (14.34)	180/1001 (17.98)	202/1011 (19.98)	352/1001 (35.16)	9/603 (1.49)	30/604 (4.97)

500 mls in one [16] and undefined in another [15]. Pooled analysis was based on any event of PPH as defined by the investigators and is shown in Fig. 2. The risk ratio (RR) of PPH with carbetocin was 0.79 (95% CI 0.66 to 0.94; $p = 0.009$). Variation in RR attributable to heterogeneity I^2 was 25.8%.

Data on additional uterotonic use was available from the 2012 patients across 7 studies. The need for additional uterotonic agents was reduced when carbetocin 100 μg was used compared to oxytocin (RR 0.57; 95% CI 0.49 to 0.65; $p < 0.001$). Heterogeneity I^2 across the studies, however was 81.7%. Although the criteria for additional uterotonic use were undefined in most of the studies, in clinical practice, any such decision would also largely depend on the surgeon's discretion and intraoperative assessment (Fig. 3).

The need for blood transfusion was also found to be significantly reduced when carbetocin was used as the prophylactic uterotonic in cesarean sections. Pooled analysis from four studies involving 1207 women showed a risk reduction of 0.31 (95% CI 0.15 to 0.64; $p = 0.002$). Heterogeneity I^2 was 37.0, reflecting moderate heterogeneity across studies (Fig. 4).

Discussion

This meta-analysis was conducted on a specific population (women undergoing cesarean section) comparing a pre-specified intervention (carbetocin versus the standard reference, oxytocin) measuring three specific outcomes of interest (postpartum hemorrhage, additional uterotonic use and transfusion).

Both reduction in the incidence of PPH and transfusion were statistically significant, with moderate heterogeneity across the studies. A previous meta-analysis had also demonstrated a trend towards lower risk of PPH (RR 0.66; 95% CI 0.42 to 1.06), although it was not statistically significant [8]. The earlier studies included in the aforementioned meta-analysis had a smaller proportion of non-elective cesarean sections, involved just over a thousand patients and variable rates of PPH of between 0.3 and 33.7%. The three additional papers we reviewed had higher overall rates of PPH, ranging between 7.7% and 41.5% [9–11]. In a recent large retrospective study involving more than 1000 patients, findings of the investigators also showed a significant reduction in PPH

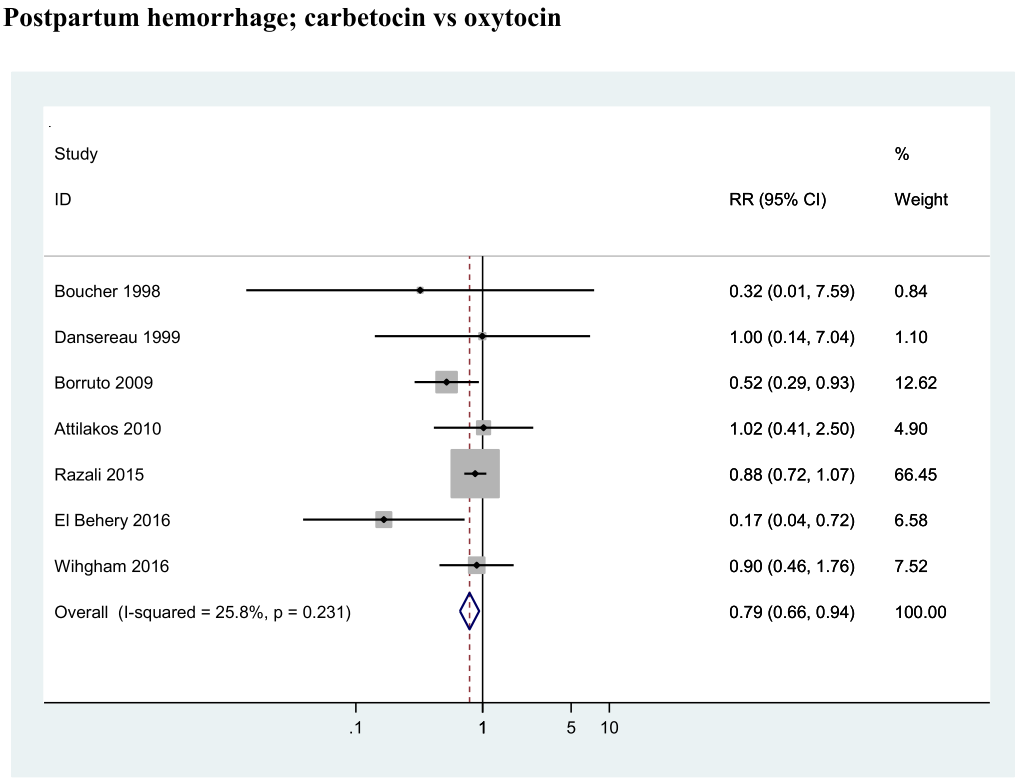

Fig. 2. Forest plots of pooled risk ratio (RR) and the corresponding 95% confidence intervals (CI) for postpartum hemorrhage. There was moderate heterogeneity across studies.

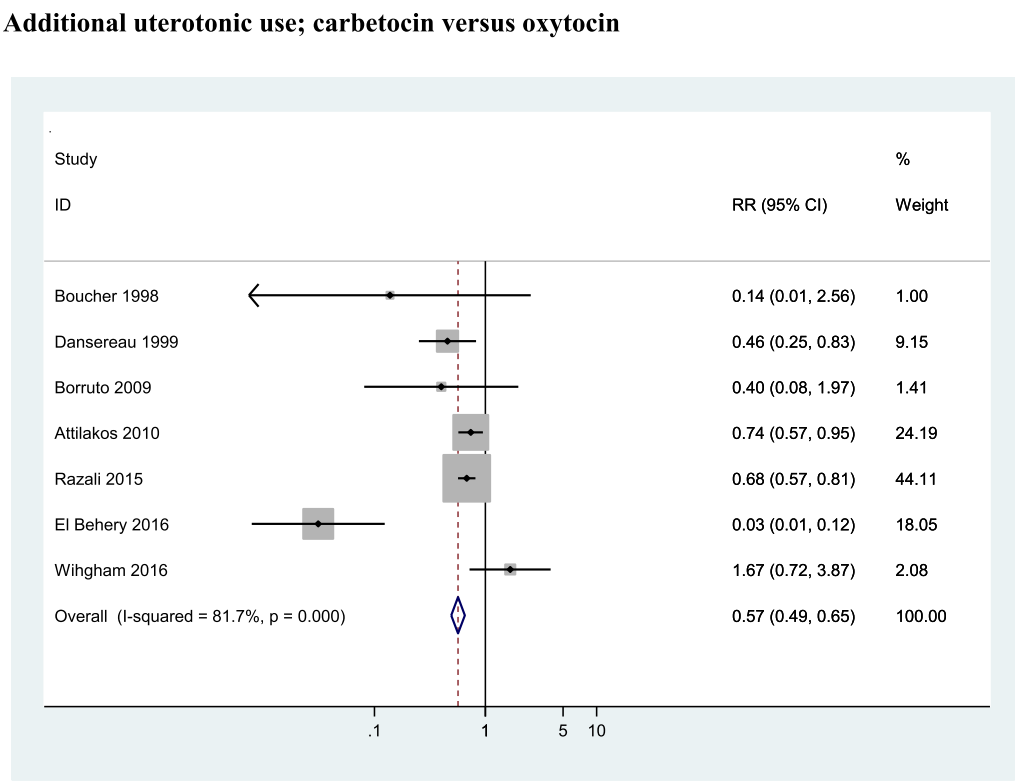

Fig. 3. Forest plots of pooled risk ratio (RR) and the corresponding 95% confidence intervals (CI) for additional uterotonic use. There was significant heterogeneity across studies.

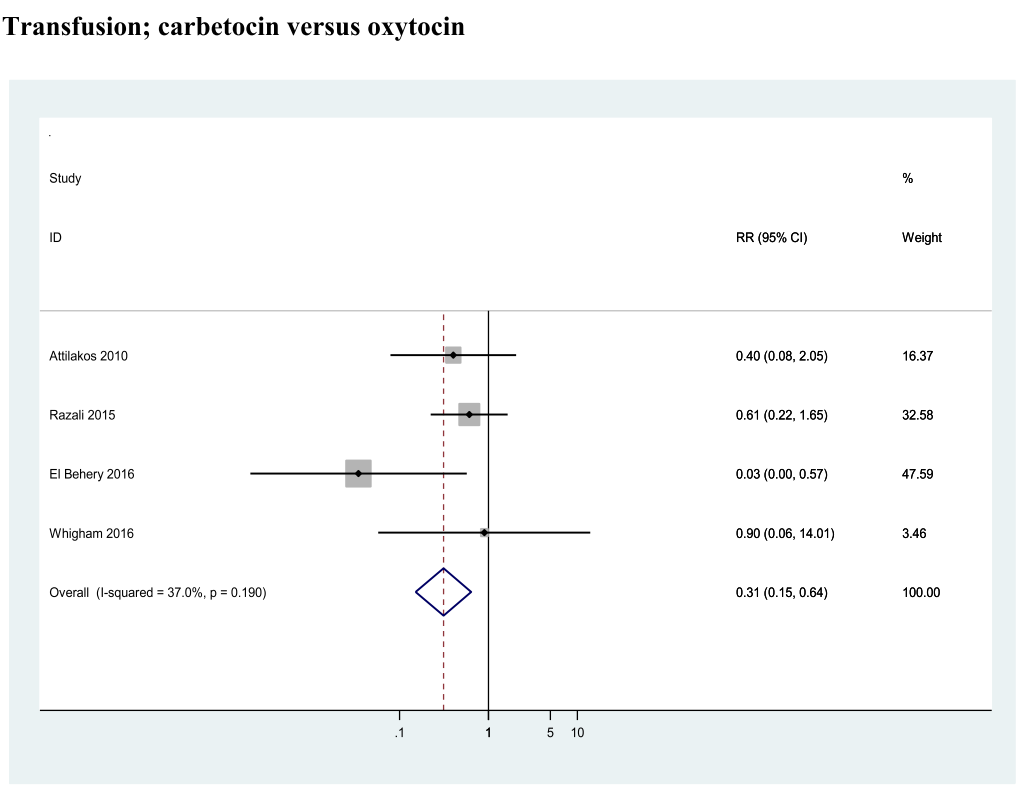

Fig. 4. Forest plots of pooled risk ratio (RR) and the corresponding 95% confidence intervals (CI) for transfusion. There was moderate heterogeneity across studies.

in women undergoing cesarean section when carbetocin was used rather than oxytocin (16.36% vs 30.45%) [9]. This was consistent with our meta-analysis. No difference was found when only the vaginal subgroup was analysed [18].

Perhaps a more significant finding was the reduction in blood transfusion requirement with the use of carbetocin. This was consistent with a previous meta-analysis which showed a trend towards reduction in transfusion, albeit not statistically significant [8]. Needless to say, the medical risks of transfusion, collection of blood products, screening and storage are labour-intensive and costly processes.

Although findings in our meta-analysis concurred with the previous meta-analysis with regards to a reduction in additional uterotonic use, there was extreme heterogeneity suggesting that pooling together of these papers were unsuitable. One reason for this heterogeneity was the variable rates at which additional uterotonics were administered across the studies as it was largely dependent on the surgeon's assessment rather than an objective criterion. In contrast, quantification of blood loss was more objective and decision for transfusion would not have been undertaken as freely as to administer additional uterotonic. Another reason for this was the variable dosage of oxytocin used across the studies, which ranged from 2 IU to 10 IU of bolus oxytocin to infusions of 20–30 IU.

Currently a vial of oxytocin (10 IU) costs USD 0.18 while a vial of carbetocin costs USD 18.20. Despite the potential benefits illustrated in this meta-analysis, the disparity between the price of carbetocin and oxytocin suggests that local or regional cost-effectiveness analysis should be performed before any decision is made to adopt it for routine prophylaxis. One reasonably strategy is to limit its use to women with a more significant risk of bleeding, such as in cases of emergency cesarean deliveries.

Looking ahead, an additional point of interest is the development of a heat-stable formulation of carbetocin, which is the subject of a randomized-controlled trial [19]. Currently, both oxytocin and carbetocin require refrigeration, limiting its use to settings where cold chain can be maintained.

Based on this contemporary meta-analysis, however, we demonstrate that carbetocin appears effective in the reduction of PPH, uterotonic use and transfusion.

Conflict of interest statement

VHY has participated in an educational conference funded by Ferring™. The rest of the authors did not report any potential conflict of interests.

Funding/support

Ferring™ did not have any influence on the design, data collection, analysis or have any input on the outcomes of the study.

Acknowledgement

The authors would like to thank the Director-General of Health Malaysia for permission to undertake this study.

Appendix 1

SEARCH STRATEGY

Medline (Pubmed)

01. carbetocin.tw
02. oxytocin agonist.tw
03. oxytocin.ti,ab
04. uterotonic.tw
05. 1 or 2 or 3 or 4
06. 5 and cesarean section
07. 5 and caesarean section
08. 5 and postpartum hemorrhage
09. 5 and postpartum hemorrhage
10. 5 and post partum hemorrhage
11. 5 and post partum hemorrhage
12. 5 and NOT vaginal.ti

Appendix 2. Quality assessment of included studies

Author	Selection bias	Blinding	Attrition and reporting bias	Other bias
Boucher et al., 1998	*Random sequence generation* Not described *Allocation concealment* Not described	*Performance and detection bias* Investigators and patients were blinded from treatment allocation. Trial drugs were administered in a similar manner	*Attrition bias* 3 out of 60 patients were excluded from analysis *Reporting bias* No intention to treat analysis	Trial was supported by a research grant from the manufacturer
	Authors' judgement Unclear risk	*Authors' judgement* Low risk of bias	*Authors' judgement* Unclear risk of bias	*Authors' judgement* Unclear risk
Dansereau et al., 1999	*Random sequence generation* Computer generated, stratified by centre and in blocks of 2 *Allocation concealment* A paired block stratified by center may allow prediction of the following patient's randomization.	*Performance and detection bias* Physician, nurses, patients and sponsor representative were blinded. Identical drugs were prepared by the pharmacist, with similar methods of administration.	*Attrition bias* 694 patients were randomized but only 635 were included in efficacy analysis. The proportion of women who were excluded due to major protocol violations were similar in both arms (12 on each arm). Decision for withdrawal of any patient was done blindly. *Reporting bias* *Intention to treat analysis was performed for safety analysis but not efficacy analysis*	Trial was supported by a research grant from the manufacturer
	Authors' judgement High risk of selection bias since allocation concealment may be ineffective	*Authors' judgement* Low risk of bias	*Authors' judgement* Unclear risk of bias	*Authors' judgement* Unclear risk

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(*continued*)

Author	Selection bias	Blinding	Attrition and reporting bias	Other bias
Borruto et al., 2009	*Random sequence generation* Not described *Allocation concealment* Not described	*Performance and detection bias* Blinding of study medication was mentioned but without elaboration. Unable to exclude bias since carbetocin was given as a bolus while oxytocinr as infusion over 2 h, unless double dummy method was used.	*Attrition bias* All 104 women randomized were included in analysis *Reporting bias* The data from all participants were included for analysis	None
	Authors' conclusion Unclear risk of bias	*Authors' conclusion* Unclear risk of performance and detection bias	*Authors' conclusion* Low risk of bias	*Authors' conclusion* Low risk of bias
Attilakos et al., 2010	*Random sequence generation* Computer generated, 1:1 ratio, blocks of 10 without stratification *Allocation concealment* Drugs used for the study were specifically prepared by a third party, independent of investigator involvement. 380 identical ampoules were sequentially numbered.	*Performance and detection bias* Random allocation sequence were only revealed to investigators at the end of the study, prior to analysis	*Attrition bias* All 377 women randomized were included in analysis *Reporting bias* Intention to treat analysis was planned and performed	At least 2 of the authors have received travel expenses from the manufacturer
	Authors' judgement Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Unclear risk of bias
Razali et al., 2016	*Random sequence generation* Computer generated, 1:1 ratio, blocks of 4 without stratification *Allocation concealment* Numbered opaque packets containing the allocated study drug was prepared by one of the co-authors who was not involved in recruitment.	*Performance and detection bias* Numbered packets kept in operating theater. Original ampoules were covered with white opaque sticker to sustain blinding for both surgeon on anaesthetist.	*Attrition bias* Of the 600 women randomized, 547 were available for analysis. 24 were excluded from the carbetocin arm and 29 were excluded from the oxytocin arm (8% vs 9.6%). Reasons for this were clearly described. Majority were because prepared drug ampoules were not given by anaesthetist. *Reporting bias* Post hoc reporting of rescue and "prophylactic" additional uterotonic use.	150 ampoules of carbetocin were provided by the manufacturer
	Authors' judgement Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias
El Behery et al., 2016	*Random sequence generation* Computer generated. *Allocation concealment* Opaque envelope containing computer generated code to identify the patient.	*Performance and detection bias* Patients and investigators were blinded to the study drug and codes were only broken at the end of the study. A double dummy design was used as both drugs were administered differently. No mention of how drugs used in the study were concealed from the staff administering the medication.	*Attrition bias* Of the 280 women recruited, 100 did not fulfill the inclusion criteria. All 180 patients who did were included in analysis. *Reporting bias* All 180 patients were included in analysis	None
	Authors' judgement Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias
Whigham et al., 2016	*Random sequence generation* Randomization table generated from EXCEL™ *Allocation concealment* Generic study labels provided by pharmacy. Sequential ampoules, matching randomization study label, were used.	*Performance and detection bias* Patient, anaesthetist and operating surgeon were blinded until prior to analysis	*Attrition bias* Of the 114 women randomized, 112 were available for analysis. Two patients received general anaesthesia and were excluded. *Reporting bias* Data from all women who were randomized were reported	None
	Authors' judgement Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias	*Authors' judgement* Low risk of bias

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