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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