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ORIGINAL ARTICLE

Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial*

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Abstract

Objective: We compared the efficacy of Carbetocin (long-acting oxytocin receptor agonist) versus Oxytocin given at non-elective caesarean section.
Method: We performed a double-blind, randomised, single-centre study. Eligible women were ≥37 weeks of gestation undergoing emergency caesarean section. Participants received either carbetocin of 100 μg or oxytocin 5 international units. The primary outcome was the need to administer additional uterotonics, as determined by the clinician. Secondary outcomes included estimated blood loss, haemoglobin drop pre–post operation and the need for a blood transfusion
Results: From August 2012 to February 2013, 114 women were enroled. Two were excluded from analysis as they received a general anaesthetic. Fifty-nine patients received 100-μg carbetocin; 53 received 5 international units oxytocin. There was no statistically significant difference in the number of women requiring additional uterotonics between the two groups: Carbetocin group 22% and Oxytocin group 13% ($p = 0.323$). There were no significant differences in the fall in haemoglobin, estimated blood loss, rates of post-partum haemorrhage or blood transfusions.
Conclusion: Oxytocin and carbetocin have similar requirements for additional uterotonics, estimated blood loss, haemoglobin drop and blood transfusions. There was a trend towards requiring additional uterotonics in patients receiving Carbetocin which was not statistically significant. This study found no benefits in using carbetocin over oxytocin.

Keywords

Caesarean section, carbetocin, oxytocin, post-partum haemorrhage, uterotonics

History

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Introduction

Post-partum haemorrhage (PPH) accounts for 14 million cases of obstetric haemorrhage worldwide and is the leading cause of maternal death throughout the world [1]. The worldwide PPH rate estimated to be 6% [2]. Post-partum haemorrhage is associated with intensive care unit admission, increased need for blood transfusion and prolonged hospital stay [2].

The majority of PPHs are caused by uterine atony. Therefore, identifying effective agents to resolve uterine atony is paramount to reducing maternal morbidity and mortality caused by PPH [3]. Caesarean section delivery is a known risk factor for PPH [4]; improving uterine tone at caesarean section is an important parameter if rates are to be reduced. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends a single 5 international units slow intravenous injection of oxytocin to improve uterine tone at caesarean section [5].

Carbetocin is a synthetic long-acting analogue of oxytocin, used to improve uterine tone (half-life 40 min [6] versus 4–10 min [7]). Hunter et al. [8] showed that intravenous administration of carbetocin in post-partum patients resulted in a tetanic uterine contraction which commenced by 2 min and lasted 6 min. Rhythmic contractions were then produced for 60 min after carbetocin had been given. The same study further showed that an intramuscular injection produced a tetanic contraction within the same time frame with rhythmic contractions lasting approximately 119 min [8].

One previous randomised control trial involving 694 women showed that a single intravenous injection of carbetocin is more effective than oxytocin infusion for preventing uterine atony at elective caesarean section (additional uterotonic use 4.7% versus 10.1%) [9]. Carbetocin is currently licensed in Australia to prevent uterine atony at elective caesarean section. However, the efficacy of Carbetocin at non-elective caesarean section is still unclear.

Elective caesarean section is associated with extremely low blood transfusion rate when compared with vaginal birth,

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reported to be around 1% [10]. In contrast, emergency caesarean section has been shown to have a higher complication rate (14.5% versus 6.8%) [11], including higher estimated blood loss and post-partum haemorrhage rate. Therefore, it is possible that routine carbetocin administration instead of oxytocin may have greater potential benefit in the setting of emergency or non-elective caesarean section.

To examine this, we performed a double-blind randomised trial to compare the effectiveness of carbetocin and oxytocin in women undergoing non-elective caesarean section under regional block.

Materials and methods

We performed a double-blind randomised, controlled study comparing oxytocin 5 international units and 100-µg carbetocin intravenously in women undergoing a non-elective caesarean section. This was performed at one centre, Frankston Hospital. This is a secondary-level teaching hospital in Victoria, Australia with approximately 2600 deliveries per year. The trial was registered with the Australia and New Zealand clinical trials registry (ACTRN12612000466842), and ethics Committee approval was granted by the Peninsula Health Human Resources and Ethics Team (HREC/12/PH/28).

We recruited women undergoing an emergency section at Frankston Hospital. We approached women to participate in this study when they presented to birth suite for a planned induction of labour, or they were in early labour or were in active labour but had an epidural anaesthetic. Patients who were in the active phase of labour with no epidural (i.e. were considered to be in too much discomfort to provide informed consent) were not approached.

We excluded patients with multiple gestation, placental abruption or women who were under 37 weeks of gestation. We also excluded those who had a general anaesthetic for their caesarean section given carbetocin is licensed for use in Australia with regional analgesia only.

The sample size calculation was based on results reported in the Bristol study [12] conducted in elective and emergency cases. They found that 45.5% of patients in the oxytocin group required additional uterotonics. Assuming that only 26% in the carbetocin group require further uterotonics, 58 patients in each group will provide 80% power to detect the difference with two-sided alpha of 0.05.

The randomisation sequence was computer generated by the hospital pharmacy. Women were randomised to receive 5 units syntocinon (Oxytocin Sandoz, Sandoz Pty Ltd.) or 100-µg carbetocin (Duratocin, Ferring Pharmaceuticals Pty Ltd.). A randomisation table was created using the random number-generating function in EXCEL™. Pharmacy used a study label, which included study title, number and expiry date to cover the trade label. Patients, anaesthetists and operating obstetricians were blinded to the intervention drug. These ampoules were stocked in the emergency theatre fridge in boxes labelled only with the matching study label. Recruited women were randomised on entering theatre, when the next sequential ampoule was taken out of the fridge. The study drug was administered immediately after birth of the baby. The randomisation was revealed to the investigators once recruitment was completed and analysis was to begin.

We collected details on parity, age, gestation, body mass index indication for caesarean section, pre-operative haemoglobin, cervical dilatation at time when the decision was made to perform a caesarean section.

Our primary outcome was the need for additional uterotonics. Our secondary outcomes included estimated blood loss during surgery, secondary post-partum blood loss and post-operative haemoglobin.

The need for additional uterotonics, uterine massage and blood transfusion were analysed using Fisher's Exact Test. Estimated Blood loss, age and weight were analysed using Student's *t*-test.

Results

Recruitment and randomisation took place between 28 August 2012 and 3 February 2013. Women who were eligible to take part in the study were approached for consent in antenatal clinic and on the labour ward. A total of 220 non-elective caesarean sections were performed during the period of the study. In total, 171 women were consented for the trial, of these 114 went on to have a non-elective caesarean section. Two patients' results were excluded because they received a general anaesthetic (Figure 1). Throughout the study, eight ampoules were discarded due to shattering of the glass into the ampoule on opening them. These patients therefore received the usual uterotonic as per Peninsula health protocol and were excluded from the study. There were no adverse events reported.

Fifty-nine (52.7%) women were randomised to receive carbetocin; 53 (47.3%) were given Oxytocin. The two groups were well matched for demographics and clinical factors

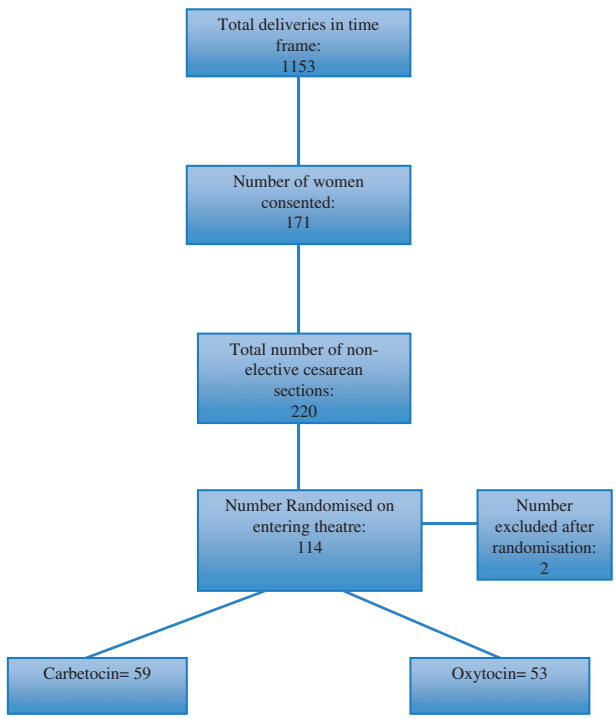

Figure 1. Flowchart.

including age, BMI, gestation and cervical dilatation at time of decision for caesarean section (Table 1).

There was no difference in the number that required further uterotonics after the bolus of either oxytocin or carbetocin was administered. In fact, there was a possible trend towards increased use of further uterotonics in the carbetocin group: 22% in the carbetocin group received an additional uterotonic agent ($n = 13$) compared 13.2% to the oxytocin group ($n = 7$; $p = 0.323$; Table 2).

There was no difference between the two groups in the rates of blood transfusion, ($n = 1$ in both groups). The need for uterine massage intra-operatively or the estimated blood loss reported by the obstetrician (mean 586 versus 561 mls). Both groups had a haemoglobin drop of 1.8 g/dL between blood taken before and after the caesarean section (Table 2).

There was no difference in rates of PPH (defined as estimated blood loss >1000 ml) was equal between groups 12% of the carbetocin group ($n = 7$) and 15% in the oxytocin group ($n = 8$; Table 3).

A subgroup analysis was undertaken in 58 women who had a cervical dilatation of 4 cm or more at time of caesarean section (Table 4). This is active labour as defined by the National Institute of Clinical Excellence (NICE) guidelines [13]. In the Carbetocin group, 30 women were found to be in active labour with 10 requiring additional uterotonics (33%). Twenty-eight women in the oxytocin group were 4 cm or more dilated with four requiring additional uterotonics (14%).

Table 1. Demographics and clinical factors.

	Carbetocin $n = 59$	Oxytocin $n = 53$
Age (years), mean (SD)	28.3 (5.9)	28.9 (5.8)
BMI, mean (SD)	27.6 (7.2)	27.7 (6.1)
Gestation (weeks)	39.6(1.5)	40.0 (1.4)
Cervical dilatation (cm), median(IQR)	4 (1–7)	4 (2–6)
Anaesthetic type		
Epidural	24 (40.7%)	15 (28.8%)
Spinal	35 (59.3%)	37 (71.2%)
Parity		
Nulliparous	37 (62.7%)	30 (56.6%)
Multiparous	22 (37.3%)	23 (43.4%)
Pre-operative HB, mean(SD)	12.9 (1.1)	12.8 (1.3)
Reason for C/S		
Failure to progress	25 (42.4%)	16 (30.2%)
Fetal distress	14 (23.7%)	18 (34.0%)
Failed IOL	5 (8.5%)	5 (9.4%)
Prev C/S	8 (15.6%)	7 (13.2%)
Booked elective C/S in labour	7 (11.9%)	7 (13.2%)

SD: standard deviation; IQR: interquartile range; Hb: haemoglobin; C/S: caesarean section; IOL: induction of labour.

Table 2. Blood transfusion, haemoglobin drop and number patients who received additional uterotonics.

	Carbetocin	Oxytocin	p values
Additional uterotonic agent (number of women)	13 (22.0%)	7 (13.2%)	0.323
Estimated blood loss (ml) (mean)	586	561	0.591
Haemoglobin drop g/dL (mean)	1.76	1.82	0.784
Blood transfusion (number of women)	1	1	

Comments

Our study compared the need for additional uterotonics at non-elective caesarean section after initial use of either carbetocin or oxytocin. We found no difference in additional uterotonic use between the two groups. There was also no significant difference in the other clinical indicators of blood loss, such as post-partum haemorrhage rate, estimated blood loss or drop in haemoglobin between the two groups.

Ours is the first randomised trial specifically examining the potential efficacy of carbetocin administering at non-elective caesarean section. Previous studies comparing oxytocin and carbetocin have included both elective and emergency caesarean sections.

Attilakos et al. [12] examined both emergency and elective caesarean sections but did not report a subanalysis of the effects of carbetocin on those who had an emergency caesarean section. In fact, most of the patients in that trial had an elective caesarean section [12]. They found a reduced number of additional uterotonics were used in the carbetocin (100 μg) group compared with an oxytocin (5 IU) bolus. They examined the same doses of uterotonics as our study. Another trial by Dansereau et al. [9] examining only elective caesarean sections also concluded that a carbetocin bolus compared with an oxytocin infusion results in less use of further uterotonics. They also found no difference in haemoglobin drop or post-partum haemorrhage rate. The study compared a 100-μg bolus of carbetocin with a 5-unit oxytocin bolus plus an 8-h infusion of oxytocin. Thus, both trials suggest carbetocin appears to reduce the need for additional uterotonics at elective caesarean section. It is perhaps surprising that in our

Table 3. Number of women with blood loss ≥1000 ml.

	Carbetocin (number of women)	Oxytocin (number of women)
Blood loss ≥1000 ml in theatre	6	5
Blood loss ≥1000 ml in 24 hrs (inc in theatre)	7	8

Table 4. Number of women requiring additional uterotonics early versus active labour.

	Overall			Carbetocin			Oxytocin		
	Dilatation ≥4 cm ($n = 58$)	Dilatation <4 cm ($n = 54$)	p value	Dilatation ≥4 cm ($n = 30$)	Dilatation <4 cm ($n = 29$)	p value	Dilatation ≥4 cm ($n = 28$)	Dilatation <4 cm ($n = 25$)	p value
Additional uterotonic	14 (24.1%)	6 (11.1%)	0.072	10 (33.3%)	3 (10.3%)	0.057	4 (14.3%)	3 (12%)	1.00

trial which exclusively examined non-elective caesarean section deliveries, we did not find a benefit.

However, there has been one further trial by Borruto et al. [14] which did not find carbetocin was of benefit. That study compared a carbetocin bolus with a 2-h oxytocin infusion and they included both elective and emergency caesarean section deliveries. They concluded that carbetocin was as good as oxytocin in maintaining uterine tone and limiting blood loss, with no statistical significant difference in additional uterotonic use or blood loss. We drew the same conclusion in our study where we only examined non-elective caesarean section deliveries.

One recent trial compared the use of carbetocin 100-μg iv injection with an oxytocin infusion of 20 units in 1-l ringers lactate at emergency caesarean section in obese women in active labour. They found significantly less post-partum haemorrhage, additional uterotonics and better contractility in the carbetocin group. However this trial did not explicitly define active labour and only examined outcomes in nulliparous women; although contrary to our findings, they cannot be compared [15].

Of note, the cost of oxytocin is AU$3 compared, which is 10-fold cheaper than carbetocin (AU$31). Considering we found no difference in outcomes, this may have significant economic implications. In light of our trial, we would suggest that it would be economically reasonable that institutions continue to use oxytocin instead of carbetocin as the uterotonic of choice at non-elective caesarean section deliveries.

A potential limitation to our study is that there was a low incidence of using additional uterotonic agents, considerably less than the figure on which we based our power calculation. .This may mean our study may be underpowered to detect a smaller difference. Nevertheless, we note our study identified a trend towards the need for more additional uterotonics in the carbetocin group.

We conclude that there are no benefits to the use of carbetocin over oxytocin in emergency caesarean sections. We suggest 5 units of oxytocin by slow intravenous injection should continue to be used at non-elective caesarean deliveries.

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Declaration of interest

The authors report no conflict of interest.

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