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Carbetocin versus oxytocin for prevention of post-partum haemorrhage at caesarean section in the United Kingdom: An economic impact analysis

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A B S T R A C T

Objective: To determine the economic impact of the introduction of carbetocin for the prevention of postpartum haemorrhage (PPH) at caesarean section, compared to oxytocin.
Study design: The model is a decision tree conducted from a UK National Health Service perspective. 1500 caesarean sections (both elective and emergency) were modelled over a 12 month period. Efficacy data was taken from a published Cochrane meta-analysis, and costs from NHS Reference costs, the British National Formulary and the NHS electronic Medicines Information Tool. A combination of hospital audit data and expert input from an advisory board of clinicians was used to inform resource use estimates. The main outcome measures were the incidence of PPH and total cost over a one year time horizon, as a result of using carbetocin compared to oxytocin for prevention of PPH at caesarean section.
Results: The use of carbetocin compared to oxytocin for prevention of PPH at caesarean section was associated with a reduction of 30 (88 vs 58) PPH events (>500 ml blood loss), and a cost saving of £27,518. In probabilistic sensitivity analysis, carbetocin had a 91.5% probability of producing better outcomes, and a 69.4% chance of being dominant (both cheaper and more effective) compared to oxytocin.
Conclusion: At list price, the introduction of carbetocin appears to provide improved clinical outcomes along with cost savings, though this is subject to uncertainty regarding the underlying data in efficacy, resource use, and cost.

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Introduction

Primary Post Partum Haemorrhage (PPH) is most commonly defined as blood loss of 500 ml or more from the genital tract within 24 h of childbirth [1]. Uterine atony is the cause of up to 90% of PPH and is increasing [2]. Prophylactic uterotonic drugs are part of the active management of the third stage of labour that reduces risk of PPH by 66% when compared with physiological management [3], and a World Health Organisation (WHO) study concluded that haemorrhage prevention programmes should focus on the use of uterotonic drugs [4].

The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom currently recommend oxytocin (Syntocinon®, Alliance) as the uterotonic drug of choice for PPH prophylaxis: a 10IU intramuscular dose for vaginal births [5] and a 5IU slow intravenous dose for caesarean births [6]. Carbetocin (Pabal®, Ferring) is a synthetic analogue of oxytocin, with structural modifications that increase its half-life and duration of action [7]. A Cochrane review [8] concluded that use of carbetocin resulted in a statistically significant reduction in the use of additional uterotonic drugs at caesarean section when compared with oxytocin and a numerical reduction in the incidence of PPH. Although carbetocin is likely to be at least as clinically effective as oxytocin, it is more expensive, with little published evidence on the cost-effectiveness of its use – as highlighted by the Cochrane review [8]. The data that does exist is conflicting and of variable quality [9–11].

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In this paper we describe the use of a health economic model constructed to assess the cost-effectiveness of carbetocin for PPH prophylaxis at caesarean section from the perspective of the UK National Health Service.

Methods

A decision tree was constructed in Microsoft Excel 2010® to model prophylactic doses of 5 IU intravenous oxytocin, or a single prophylactic (100 μg) dose of intravenous carbetocin at caesarean section for PPH prevention. Oxytocin and Carbetocin were selected for comparison as they represent current UK prophylactic uterotonic practice and a longer lasting and potentially more effective (but more expensive) alternative, respectively. The evaluation was undertaken from a National Health Service perspective, in keeping with UK National Institute for Health and Care Excellence recommendations [12].

The primary outcome measures were the number of PPH events prevented and the impact on total cost incurred by a large maternity unit over a one year time horizon, as a result of using carbetocin instead of oxytocin for PPH prevention at caesarean section. The study population comprised all women undergoing elective and emergency caesarean section. The number of caesarean sections performed in the model was set to 1500, based on a unit with approximately 6500 deliveries per annum (a caesarean section rate of about 24%). Hospital-level audit data was used to inform estimates of resource use.

Treatment pathway

The modelled treatment pathway is shown in Fig. 1. Patients undergoing caesarean section receive a prophylactic uterotonic drug after their delivery. Despite this prophylaxis, some women experience uterine atony requiring additional uterotonic drugs that will prevent PPH in some, but not all cases. Patients experience varying volumes of blood loss at caesarean section – in the model this is captured in 4 health states – 'No PPH event', 'PPH 500–999 ml', 'PPH 1000–1499 ml' and "PPH > 1500 ml". Larger volumes of blood loss are associated with more treatment and resource use, and as a result are more expensive. Table 1 shows the inputs to the model by different levels of blood loss.

Patients are monitored in recovery for 2 h after their caesarean section, as recommended by national guidelines [6]. Patients requiring additional uterotonic drugs (e.g. 4 h oxytocin infusion) stay in recovery, or on labour ward, for longer. In these areas staff to patient ratios are greater, and more medical time is utilised. Patients who experience a large PPH are more likely to require postnatal follow up, and for their care to be discussed at a risk management forum. A combination of published data and hospital-level data was used in the economic model (Table 2).

Clinical effectiveness

Relative clinical efficacy was obtained from a published Cochrane Collaboration *meta*-analysis of four randomised control trials of carbetocin and oxytocin for PPH prophylaxis at caesarean section [8]. Data used included the rate of PPH and the proportion of patients requiring additional uterotonic drugs (Table 3). Point estimates (published means) have been used in the base case, with probabilistic estimates also presented, as the Cochrane review concluded that although the reduction in the use of additional uterotonic drugs was statistically significant, the estimate for differences in PPH rates was not (p = 0.086). The use of values (even if statistically insignificant), with a confidence interval around their estimates is well established in health economics [13], as such estimates provide a the best estimate to the real world, where evidence is not always clear and is associated with uncertainty regardless of the significance of the finding.

Fig. 1. Treatment pathway.

Table 1
Proportionate spread of PPH events across categories of blood loss.

		Proportion of all PPHs falling in each category				Total
		No PPH (blood loss <500ml)	500–999ml	1000–1499ml	≥1500ml	
Holleboom 2013	Oxytocin	680	319	66	57	1122
	Carbetocin	248	165	33	16	462
Raw data from published literature						
Su 2012	Oxytocin	563	35			598
	Carbetocin	574	23			597
Model inputs, including interpolation of missing data using data from the Holleboom et al., dataset						
Su 2012	Oxytocin	94.20%	4.30%	0.90%	0.70%	100%
	Carbetocin	96.20%	2.80%	0.60%	0.40%	100%

Table 2
Cost and resource use inputs for PPH events.

	Resources needed for management of PPH in each category			Source of resource use estimate
	PPH 500–999 ml	PPH 1000–1499 ml	PPH ≥1500 ml	
Additional uterotonic drugs given to treat PPH (cost taken from BNF volume 67)				
Oxytocin 5iU (Syntocinon®, £0.80)	1	1	1	Expert opinion *(see footnote)*
Ergometrine 0.5IU and Oxytocin 1 ml (Syntometrine®, £1.35)	0	1	1	Expert opinion
Carboprost 250 µg (Haemobate® £18.20)	0	1	3	Expert opinion
Intravenous replacement (cost take from sources as stated)				
Hartmann's solution 500 ml IV (£2.75 – Just Care Medical)	1	3	5	Expert opinion
Red blood cells, 1 unit (£122.09 – NHS Blood & Transfusion Services)	1.5%, mean 2.3 units	7.5%, mean 2.1 units	23%, mean 2.6 units	NHS Trust data
Fresh Frozen Plasma, 1 unit (£33.81 – NHS Blood & Transfusion Services)	0	0	2	Expert opinion
Hours of staff time needed, in addition to routine uncomplicated caesarean section (costs taken from PSSRU 2013)				
Anaesthetist (£94/h)	0	0	4	Expert opinion
Obstetrician (£100/h)	0	0	4	Expert opinion
Midwife (£65.44/h)	0	0	4	Expert opinion
Junior doctor (£29/h)	0	0	4	Expert opinion
Haematologist (£99/h)	0	0	1	Expert opinion
Other costs (costs taken from NHS Reference Costs 2012/2013)				
Additional length of post-natal inpatient stay (days), £439.35/day	0.03	0.28	1.19	NHS Trust data
Days required in high dependency unit such as 1:1 care on Labour Ward (£630/day)	0	1	1	Expert opinion
Additional cost for operating theatre per hour (£1139.60 – ISD Scotland)	0	1	1	Expert opinion
Case discussion at PPH meeting (£67.14)	0	0	1	Expert opinion
Post natal consultant follow up in first 10 post natal weeks (£129.92)	2.9%	2.6%	7.4%	NHS Trust data
Total cost per event	£17.28	£1782	£3507	

Expert opinion provided by panel of 5 anaesthetists, 5 obstetricians and 2 midwives.

Table 3
Clinical effectiveness estimates used in the economic model.

Source	PPH rate			Use of additional uterotonic drugs	
	Oxytocin	Carbetocin		Oxytocin	Carbetocin
Su 2012 (systematic review and *meta*-analysis)	5.9%	3.9%		21.5%	13.6%
	PPH defined as blood loss >500 ml "or as defined by trialist". Meta-analysis includes 4 studies; Borruto 2009 defines PPH >500 ml, Boucher 1998 and Attilakos 2010 define PPH >1000 ml, and Dansereau does not state definition.				

During the review of existing literature, we noted that the reporting of PPH categories is inconsistent: the *meta*-analysis data [8] includes analyses of both "PPH > 1000ml" (two studies), and "PPH > 500 ml or as defined by trialist" (all four studies). To account for incomplete reporting, the proportion of total PPH events in each blood loss category was interpolated from a cohort study of 1584 women in the Netherlands, which compared carbetocin and several different dosing regimens of oxytocin for PPH prophylaxis during caesarean section [14]. Data regarding the distribution of PPH events across these categories was provided by the publishing authors. The resulting data for PPH in each blood loss category for all efficacy sources is shown in Table 1, with the distribution of outcomes assumed to be the same in both arms.

Resource use

Clinical management and resource use escalates with increasing blood loss. The proportion of cases requiring additional uterotonic drugs was derived from clinical effectiveness data shown in Table 3. The additional uterotonic drug assumed was 5 IU oxytocin given by slow IV bolus, representing UK recommended clinical practice [15]. This single dose was assigned to patients

needing "additional uterotonics", as not all patients who require additional uterotonic drugs go on to experience a PPH.

The resources required to manage a PPH in each of the categories used in the economic model (500–999 ml, 1000–1499 ml and ≥1500 ml), was estimated by a multi-professional panel of clinical experts. Resource use included the type (and number of doses) of additional drugs needed, as well as staff time associated with treatment of the PPH. The resulting assumptions are shown in Table 2. These are in line with national guidance on the management of PPH [15].

Where published estimates were not available, hospital level data (from Southmead Hospital, Bristol, UK) was used to improve accuracy of resource use estimates. Hospital level data included average length of maternal inpatient stay post caesarean, proportion of patients needing a blood transfusion, units of red blood cells transfused, and provision of consultant follow-up in the first ten postnatal weeks. Each item was also calculated for blood loss in the ranges 0–499 ml (no PPH), 500–999 ml, 1000–1499 ml and ≥1500 ml (see Table 3).

Unit cost estimates

Costs were calculated in Pounds Sterling, and were taken from NHS Reference costs, the British National Formulary and the NHS electronic Medicines Information Tool (which contains the mean price paid for generic pharmaceuticals in the UK).

Utilities

To provide a common unit of comparison, utilities decrements were used for the differing levels of PPH. As no direct utility values were available, estimates for the disutility of gastrointestinal bleeds [16] were used, such as a disutility of 0.06 for 7 days for PPH 500–1000 ml, a disutility of 0.25 for 10 days for PPH 1000–1500 ml, and a disutility of 0.25 for 14 days for PPH > 1500 ml.

Results

Table 4 contains a breakdown of costs associated with the use of oxytocin or carbetocin for prevention of PPH at caesarean section in this model. In the base case, the use of carbetocin shows a reduction of 30 PPH events (58 vs 88) and an estimated cost saving of £27,518.41 (£2,085,989 vs £2,113,508). This difference is mainly driven by a reduction in the number of PPH events (incremental cost saving £35,985) and the resultant reduction in time spent in recovery after treatment of PPH (incremental cost saving of £12,783). These savings offset the increased drug cost of carbetocin compared to oxytocin (unit price £17.64 v £0.80, which gives an increase of £22,860 per year).

Table 4
Overall cost as a result of using either oxytocin or carbetocin for prevention of post partum haemorrhage at caesarean section.

	Oxytocin	Carbetocin	Change with Carbetocin
PPH 500–1000 ml events	65	43	−22
PPH 1000–1500 ml events	13	9	−5
PPH > 1500 ml events	10	6	−3
PPH Events	**88**	**58**	**−30**
	Oxytocin	**Carbetocin**	**Change with carbetocin**
PPH Events	£105,227	£69,242	−£35,985
PPH prophylaxis	£3600	£26,460	£22,860
PPH re-treatment	£3600	£2250	−£1350
Ante-Natal	£124,312	£124,312	£0
Recovery	£1,774,419	£1,761,637	−£12,783
Follow up	£102,351	£102,090	−£261
Total cost	**£2,113,508**	**£2,085,990**	**-£27,518**

Probabilistic sensitivity analysis, which takes into account the uncertainty in input values (both clinical and cost) shows carbetocin to be more effective than oxytocin in 91.5% of scenarios, and dominant (both cheaper and more effective) in 69.4% of scenarios. When attaching utility values to PPH events based on assumed disutilities, carbetocin is cost-effective at a threshold of £20,000 per QALY in 70.5% of scenarios (Fig. 2).

Discussion

Main findings

The model demonstrates that carbetocin is likely to provide superior clinical outcomes (by reducing the rate of PPH events), along with a cost saving. However probabilistic analysis illustrates uncertainty due to the underlying data, where carbetocin does not provide cost savings (30.4%), and does not show cost-effectiveness using the NICE threshold for recommendation (over £20,000 per QALY gained, 29.5% of scenarios).

Strengths and limitations of the study

The treatment pathway used in the model is in line with national guidelines [5,6,15]. The results should be applicable to most maternity units in the United Kingdom, regardless of size, as well as those internationally with similar care pathways. Whilst UK guidelines recommend a single 5IU oxytocin dose for PPH prophylaxis, we are aware that practice varies greatly [17,18], and that there is some evidence suggesting that the addition of a postoperative oxytocin infusion may further reduce risk of PPH [19],as is common in other countries [20]. This does not affect our conclusions however; using a 40IU infusion over 4 h for all oxytocin patients increased the cost saving of carbetocin to £31,118 (an increase of approximately £3600).

Our analysis is primarily influenced by the clinical effectiveness data chosen for each scenario. Cochrane meta-analysis data was used to inform the base case, which raises the question of the methodological differences and clinical heterogeneity between studies. An important difference was the variability in the method of IV oxytocin administration in each individual study [21–24]. Each study referred to their method of oxytocin infusion as "standard", suggesting that the routine dose and administration method for prophylactic oxytocin differs between settings, and over time. Ultimately, a meta-analysis provides the best available clinical evidence whilst also reflecting some of the variability in clinical practice. A similar limitation is that adverse events were not included in the model; in the absence of a definitive head to head trial, the variation in reporting and treatment of adverse events in heterogeneous trials would introduce a bias of unknown magnitude and direction. This is particularly the case as the treatments are given alongside a complex pathway of interventions; isolating the adverse events of PPH prophylaxis would be extremely difficult.

Although necessary for resource use analysis, the sub-categorisation of PPH by blood volume does place arbitrary limits on a continuous outcome. As such, the categories have been created based on the literature available, and resources assigned to reflect the mean for patients falling within each category. We are mindful that exceedingly large PPHs may incur additional costs such as use of Factor VII, admission to Intensive Care, and potentially medico-legal expenses associated with litigation, however no data exist on these rare events and as such they have been omitted from our estimates so as not to bias the analysis. A further assumption in the model is that the breakdown of PPH events into the different categories is assumed to be identical between the two treatments (as is the proportion of patients with
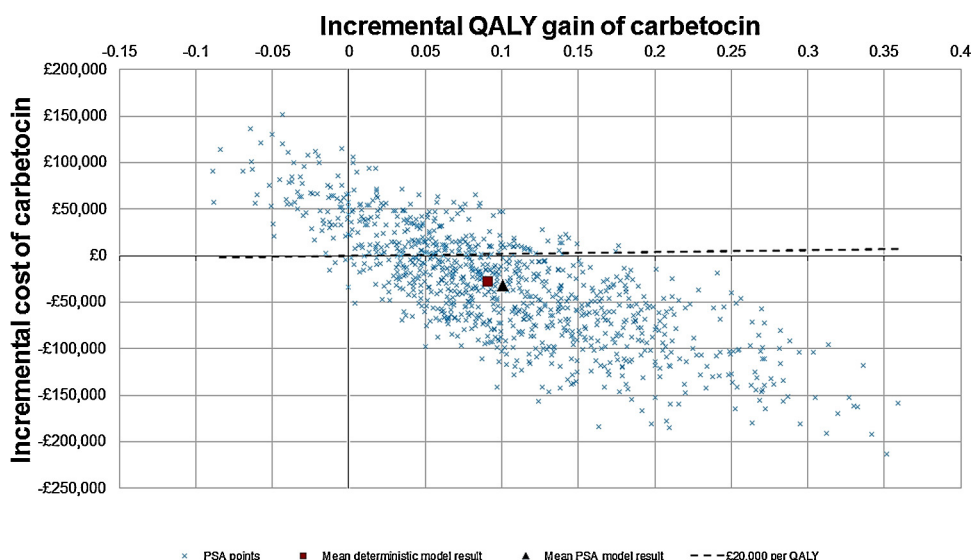
Fig. 2. Scatterplot of Monte-Carlo estimates (1000 simulations).

additional PPH risk factors such as obesity, prolonged labour and placenta praevia). This is representative of clinical practice – PPH is not treated differently based on the prophylactic treatment received.

The lack of universally adopted categories of PPH that clinical trials use to classify obstetric blood loss also causes uncertainty in the clinical data, which is carried through to modelling. Although the most commonly used definition of PPH is that quoted by the WHO (loss of >500 ml blood from the genital tract within 24 h of birth), the outcomes reported in clinical trials vary considerably, particularly for trials involving caesarean section. As trials commonly only report blood loss in one of these categories (e.g. "PPH > 1000 ml", or PPH ">500 ml"), missing category data was accounted for by the interpolation of categorical PPH proportions from a large published dataset [14]. These data are from a large study population in a healthcare system comparable with that of the UK. However, this dataset only included elective caesarean sections, whereas PPH, particularly severe PPH, is more common following emergency caesarean section [25–27].

Interpretation in light of existing literature

A small study [11] performed a financial evaluation alongside a departmental audit in a UK hospital, after changing from routine use of oxytocin to carbetocin at elective caesarean section. This was an observational study which only contained 24 patients in the oxytocin arm, and 37 patients in the carbetocin arm. It concluded that carbetocin was associated with a £18.52 increased cost per patient, and no significant clinical benefit. In addition to the small sample size and lack of formal methods for adjusting for difference in baseline patient characteristics, it is not clear how these costs were estimated, and no formal economic modelling was performed. Similarly a Mexican abstract [9] reported an economic evaluation of carbetocin for the prevention of uterine atony in patients with risk factors for PPH. This compared carbetocin with oxytocin, and included a total of 152 patients. Mode of delivery was not stated, nor were details of any blinding, costs included, or treatment pathways used. It concluded that the overall cost per patient treated with carbetocin was 529 USD less than those treated with oxytocin (approximately £339 per patient). However without further information about the study, resource use, or the costs included, comparison with our results is not meaningful.

A more useful comparison is with a cost-minimization analysis performed from a Canadian healthcare system perspective [10] which investigated the use of carbetocin for prevention of PPH during elective caesarean section, with treatment pathways modelled on guidelines from the Society of Obstetricians and Gynecologists of Canada. This compared carbetocin with unnamed "comparators most commonly encountered in clinical practice". Rather than using clinical trial data the study "assumed that the incidence of PPH was equal between treatment strategies", which will have heavily influenced results and is inconsistent with economic evaluation guidelines [13]. This analysis reported a per patient cost of $31.95 for carbetocin vs $32.31 for oxytocin. While these results are more consistent our results, it is again difficult to draw comparisons due to the limited information presented, and assumption of equal efficacy in prevention of PPH (contrary to published *meta*-analytic data).

Conclusions

This economic evaluation combines the best available clinical effectiveness data for the use of oxytocin versus carbetocin during caesarean section for PPH prophylaxis, with UK hospital-level resource use data. The model estimates that carbetocin is likely to result in better clinical outcomes and a modest cost-saving when compared to oxytocin, albeit with substantial uncertainty.

Whilst the results of this model will help to inform policy makers, further work is needed. The current data indicate carbetocin is more effective than oxytocin in reducing the use of additional uterotonic drugs, and although existing data indicates a numerical advantage for carbetocin in reducing the rate of PPH, this does not reach statistical significance. There exists therefore uncertainty in the relative clinical effectiveness of carbetocin, which we hope will be provided by an ongoing randomised control trial ("The IMox Study", Clinicaltrials.gov NCT02216383).

Although carbetocin appears to have a number of advantages in our study (potentially including cost), a large randomised trial of the use of these drugs at caesarean section with parallel health economic evaluation, is required to conclusively inform practice. Until this has been conducted, the evaluation presented here uses the most robust information available and demonstrates that the introduction of carbetocin is likely to result in better clinical outcomes and potentially a modest per patient cost-saving, albeit with uncertainty. At the very least, it appears that carbetocin use

would be cost-neutral, meaning decisions regarding its introduction should be based on clinical effectiveness.

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Detail of ethical approval

Ethical approval was not required for this project.

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