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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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Disclosure and contribution of authorship.

The project was led by HvdN, the model was developed by AJH, clinical input was provided by HvdN, TD and DS. HvdN is the lead investigator on a clinical study that has received start up funding from Ferring (the manufacturers of carbetocin), TD has attended advisory board meetings sponsored by Ferring. DS has attended expert meetings organised by Ferring and has organised events sponsored by them. AJH is an employee of BresMed, who have received funding from both Ferring and Pfizer (the manufacturers of carboprost). All authors read and approved the final manuscript.

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Abstract (Word count 240)

Objective

To determine the economic impact of the introduction of carbetocin for the prevention of post partum 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 meta-analysis, costs were taken 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 measure was the incidence of PPH in a department 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 (>500ml 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 clinical data and cost data.

Keywords: Cost-effectiveness, Economic model, carbetocin, postpartum haemorrhage.

Main text (Word Count 2496)

Introduction

Primary Post Partum Haemorrhage (PPH) is most commonly defined as blood loss of 500ml or more from the genital tract within 24 hours of the birth of a baby(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 reduce risk of PPH, and a World Health Organisation (WHO) study concluded that haemorrhage prevention programmes should focus on the use of uterotonic drugs(3).

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(4) and a 5IU slow intravenous dose for caesarean births(5). Carbetocin (Pabal®, Ferring) is a synthetic analogue of oxytocin, with structural modifications that increase its half-life and duration of action(6). A Cochrane review(7) 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(7). The data that does exist is conflicting and of variable quality; data from a single unit in the UK using a time-interrupted series of 165 births(8) demonstrated an increase in costs of approximately £18 per caesarean section with little clinical benefit, whereas data from the Mexican department of Social Security(9) demonstrated savings of nearly \$500 (US) per caesarean section.

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.

Methods

A decision tree was constructed in Microsoft Excel 2010® to model prophylactic doses of 5 IU intravenous oxytocin, or a single prophylactic (100µg) 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. This economic evaluation was undertaken from a National Health Service perspective, in keeping with UK National Institute for Health and Care Excellence recommendations for technology appraisal(10).

The primary outcome measures were the number of PPH events prevented and the incremental 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 and 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 Figure 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 500-999ml’, ‘PPH 1000-1499ml’ and “PPH >1500ml”. 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 hours after their caesarean section, as recommended by national guidelines(5). Patients requiring additional uterotonic drugs (e.g. 4 hour 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(7).

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(11), 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.

During the review of existing literature, we noted that the reporting of PPH categories is inconsistent: the meta-analysis data(7) includes analyses of both “PPH >1000ml” (two studies), and “PPH >500ml 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(12). 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 recommended clinical practice in the UK(13). 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 (500-999ml, 1000-1499ml 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(13).

Where published estimates were not available, hospital level data (from Southmead Hospital, Bristol, UK) was used to improve accuracy of resource use estimates. Data used to inform the model 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 0-499ml (no PPH), 500-999ml, 1000-1499ml 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 (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

(14) were used, such as a disutility of 0.06 for 7 days for PPH 500-1000ml, a disutility of 0.25 for 10 days for PPH 1000-1500ml, and a disutility of 0.25 for 14 days for PPH>1500ml.

Results

Table 4 is 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, with the use of carbetocin compared to oxytocin, there is 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 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 unit price of carbetocin when compared with oxytocin (unit price £17.64 v £0.80 – a total increase of £22,860 per year).

Probabilistic sensitivity analysis, which takes into account the distribution in the results, based on uncertainty in the inputs to the model (both clinical inputs, and cost), shows carbetocin to be more effective than oxytocin in 91.5% of scenarios, dominant (both cheaper and more effective) in 69.4% of scenarios, and cost-effective at a threshold of £20,000 per QALY in 70.5% of scenarios (Figure 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, where in approximately 30% of cases, carbetocin is not cost-effective using the NICE threshold for recommendation (over £20,000 per QALY gained).

Strengths and limitations of the study

The treatment pathway used in the model is in line with national guidelines(4, 5, 13). The results should be applicable to most maternity units in the United Kingdom, regardless if size, as well as those internationally with similar care pathways.

The analysis described is primarily influenced by the clinical effectiveness data chosen for each scenario. 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 (15),(16) (17)(18). Each 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.

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. 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. This is representative of clinical practice – PPH is not treated differently based on the prophylactic treatment received.

As previously highlighted, there is a lack of universally adopted categories of PPH that clinical trials use to classify obstetric blood loss. Although the most commonly used definition of PPH is that quoted by the WHO (loss of >500ml blood from the genital tract within 24 hours 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 >1000ml”, or PPH “>500ml”), missing category data was accounted for by the extrapolation of categorical PPH proportions from one large published dataset (12). These data are from a large study population in a healthcare system comparable with that of the UK. However, they only included elective caesarean

sections, whereas PPH, particularly severe PPH, is more common following emergency caesarean section(19-21).

Interpretation in light of existing literature

A small study (8) 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 but 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. It is not clear how these costs were estimated, and no formal economic modelling was performed.

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. This equals roughly £339 per patient, but without further information about the study or the costs included, comparison with our results is not meaningful.

A cost-minimization analysis performed from a Canadian healthcare system perspective(22) 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 as we have done, this 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(11). 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 rates of PPH in the abstract.

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 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 there is a numerical advantage for carbetocin in reducing the rate of PPH, this is statistically insignificant. The clinical effectiveness of carbetocin needs further investigation and an ongoing randomised control trial ("The IMox Study", Clinicaltrials.gov NCT02216383) will add to literature.

Further work is also needed to measure the effect that PPH has on patient quality of life and the effect of uterotonic drugs on quality of life. Both would advance the debate about whether carbetocin is a superior prophylactic uterotonic drug for use at caesarean section.

Although carbetocin appears to have a number of advantages (potentially including cost), a large randomised trial of the use of these drugs at caesarean section, with parallel health economic evaluation, is required to 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 possibly a modest per patient cost-saving, albeit with uncertainty. At the very least, it appears that carbetocin use would be cost-neutral, so decisions regarding its introduction should be based on its effectiveness.

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Figure and table caption list

Figure 1: Treatment pathway

Figure 2: Scatterplot of Monte-Carlo estimates (1000 simulations)

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

Table 2: Cost and resource use inputs for PPH events

Table 3: Clinical effectiveness estimates used in the economic model

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