

# Cost effectiveness analysis of carbetocin during cesarean section in a high volume maternity unit

Hian Yan Voon<sup>1</sup> , Asrul A. Shafie<sup>2</sup>, Mohamad A. Bujang<sup>3</sup> and Haris N. Suharjono<sup>4</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Sri Aman Hospital, Sarawak, <sup>2</sup>School of Pharmaceutical Sciences, University of Science Malaysia, Penang, <sup>3</sup>Clinical Research Centre and <sup>4</sup>Department of Obstetrics and Gynecology, Sarawak General Hospital, Kuching, Malaysia

## Abstract

**Aim:** To evaluate the cost effectiveness of carbetocin compared to oxytocin when used as prophylaxis against post-partum hemorrhage (PPH) during cesarean deliveries.

**Methods:** A systematic review of the literature was performed to identify randomized controlled trials that compared the use of carbetocin to oxytocin in the context of cesarean deliveries. Cost effectiveness analysis was then performed using secondary data from the perspective of a maternity unit within the Malaysian Ministry of Health, over a 24 h time period.

**Results:** Seven randomized controlled trials with over 2000 patients comparing carbetocin with oxytocin during cesarean section were identified. The use of carbetocin in our center, which has an average of 3000 cesarean deliveries annually, would have prevented 108 episodes of PPH, 104 episodes of transfusion and reduced the need for additional uterotonics in 455 patients. The incremental cost effectiveness ratio of carbetocin for averting an episode of PPH was US\$278.70.

**Conclusion:** Reduction in retreatment, staffing requirements, transfusion and potential medication errors mitigates the higher index cost of carbetocin. From a pharmacoeconomic perspective, in the context of cesarean section, carbetocin was cost effective as prophylaxis against PPH. Ultimately, the relative value placed on the outcomes above and the individual unit's resources would influence the choice of uterotonic.

**Key words:** carbetocin, cesarean section, cost effectiveness, pharmacoeconomic, post-partum hemorrhage.

## Introduction

A mother is the nexus that binds individual members of a family together and without a doubt, the death of a mother affects more than just her offspring. Sadly, more than 280 000 mothers die globally each year and post-partum hemorrhage (PPH) remains an unresolved problem, contributing to 27.1% of these deaths.<sup>1</sup> The causes of PPH are best epitomized by the four 'T's: tone (atony), tissue (retained products of conception), trauma (genital tract trauma) and thrombin (bleeding diathesis). Uterine atony is recognized as the leading underlying cause of PPH. Active management of the third stage of labor is an essential

strategy to prevent PPH, although increasingly, individual components of the care bundle, such as early cord clamping, have been questioned and their recommendation subsequently retracted.<sup>2</sup> Controlled cord traction, despite reducing the length of the third stage by several minutes, merely results in a reduction of blood loss of about 10 ml.<sup>2</sup> The benefits of basic, non-pharmacological methods, such as prophylactic uterine massage, are inconclusive, may cause maternal discomfort and do not demonstrate a significant reduction in PPH events.<sup>3</sup>

This leaves the use of uterotonics, a component of the active management of the third stage, as the only intervention consistently proven to be advantageous.

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Correspondence: Dr Hian Yan Voon, Department of Obstetrics and Gynecology, Hospital Road Sri Aman Hospital, 95000 Sri Aman, Sarawak, Malaysia. Email: vhaxyn@gmail.com

In a Cochrane review involving six trials and more than 4200 women, the prophylactic use of uterotonics reduced the incidence of PPH by 50% when compared to the placebo. Similarly, the need for therapeutic uterotonics was halved when oxytocin was administered as prophylaxis.<sup>4</sup> Oxytocin, a nonapeptide analogous to the hormone secreted from the posterior pituitary is the recommended oxytocic agent because of its efficacy and tolerability.<sup>2,5</sup> It possesses a short half-life of 5 min and produces uterine contractions within 2 min, by binding to the myometrial receptors. Commercially available oxytocin can be given as a bolus intramuscularly, intravenously or as an infusion and is cheap, but requires refrigeration between 2–8°C. Side effects from oxytocin include water retention with prolonged infusion as a result of its weak vasopressin-like effects, hypotension, flushing and reflex tachycardia.<sup>6</sup>

Carbetocin is homologous to oxytocin and has a similar onset of action but a longer half-life of 40 min. This results in sustained uterine contractions for over an hour and obviates the need to maintain uterine tone with additional oxytocic infusion.<sup>7</sup> It can also be administered either as slow intravenous injection or intramuscularly, although the latter has not received approval from the United States Food and Drug Administration.<sup>8</sup> Meta-analysis has shown that when compared to oxytocin, carbetocin reduced the need for additional uterotonics. This may translate into savings in terms of lower staffing time taken to monitor and administer the additional medication.<sup>8</sup> From a practical point of view, a newer formulation of carbetocin that is stable under room temperature has been developed and this would widen its appeal, especially in settings where cold chain poses a challenge. However, this formulation is still the subject of an ongoing randomized control trial.<sup>9</sup>

Ergot alkaloids, on the other hand, are not superior to oxytocin but are associated with significant maternal side effects, with a more than twofold increase in elevated blood pressure and a fivefold increase in nausea and vomiting.<sup>10</sup> When compared to combinations containing both oxytocin and ergometrine, carbetocin has been shown to reduce the amount of blood loss with lower incidences of nausea and vomiting.<sup>8</sup>

Carbetocin has similar types and frequencies of occurrence of side effects compared to oxytocin, as detailed above, because both medications are structurally related and possess mild antidiuretic properties. One potential disadvantage as a result of its long

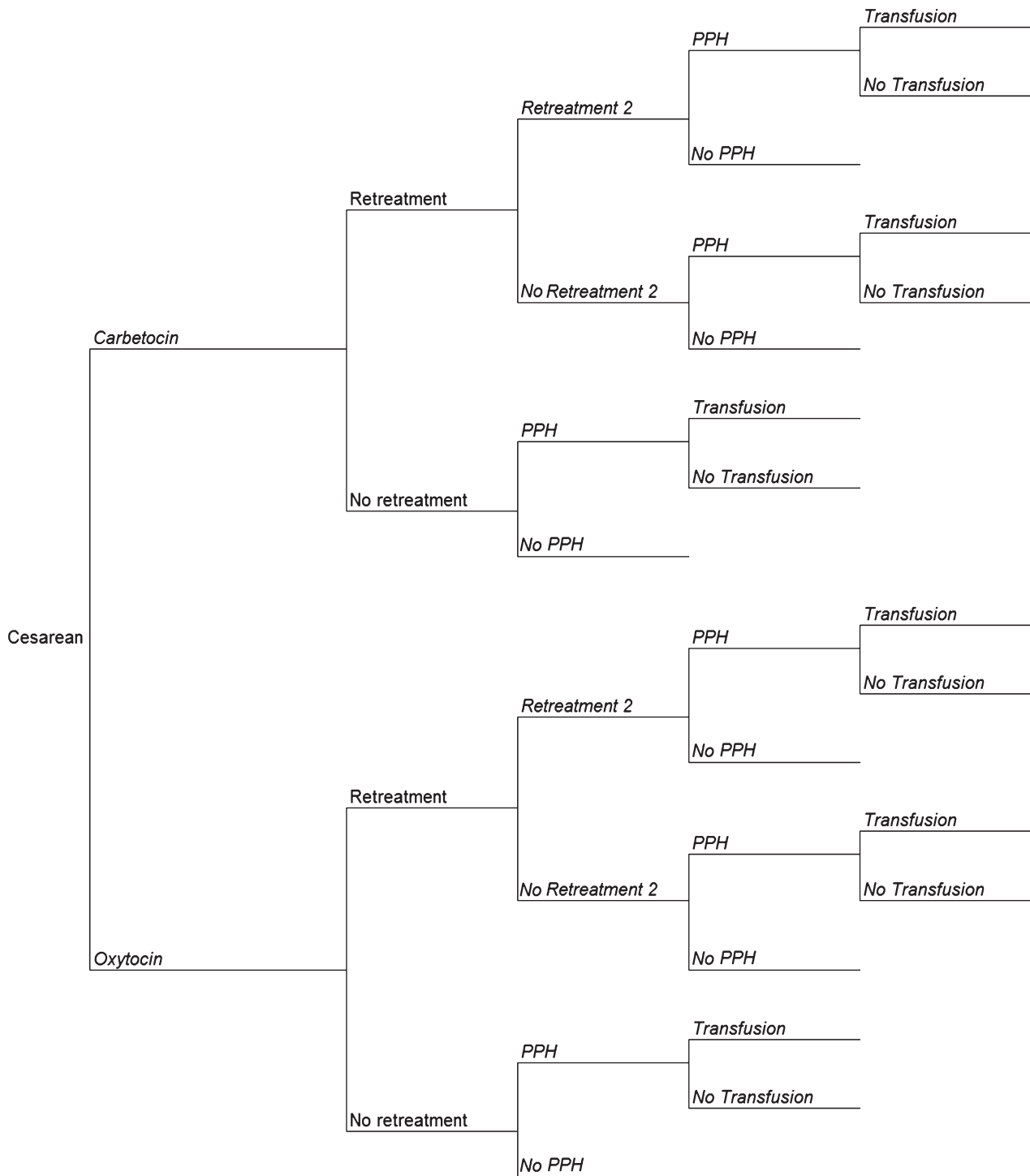
acting nature is that merely discontinuing the medication does not cease the uterine contractions produced by carbetocin.<sup>7</sup> The milk to plasma ratio of carbetocin measured by radioimmunoassay up to 6 h after administration appears reassuringly lower than the commonly accepted, albeit arbitrary threshold of 10%.<sup>11</sup>

The simplicity in administration of carbetocin and the reduction of additional uterotonics is an important consideration in reducing human errors, especially in settings where patient turnovers are high or staffing shortages arise. In view of the lower retreatment rate and the omission of preparation and monitoring of prolonged infusion, there are potential savings in terms of better utilization of staff time and lower risk of drug administration errors. This study therefore aims to examine the cost effectiveness of carbetocin compared with oxytocin after cesarean section, in a tertiary unit with high volumes of delivery.

## Methods

The cost effectiveness analysis was conducted from the perspective of a unit within the Malaysian Ministry of Health, over a period of 24 h, for the prevention of PPH. The analysis was conducted using a decision tree that rolled back the expected value of patients who received either intravenous carbetocin 100 mcg or oxytocin 5 IU (Fig. 1). Patients who required additional uterotonic, experienced PPH or received blood transfusions were calculated based on probabilities estimated from existing literature. As a prerequisite to constructing the decision tree, a literature review was performed via 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) from its inception until May 2016. Two authors independently performed the literature review, which was then crosschecked. Studies comparing the clinical outcomes and complications between the use of carbetocin and oxytocin were identified. Only randomized controlled trials were included. Studies involving the use of carbetocin or oxytocin in vaginal deliveries were excluded. No language restrictions were applied.

The cost of procuring the medications and equipment required to administer the medications, such as intravenous giving sets and crystalloids, were obtained from the inventory of the Pharmaceutical



**Figure 1** Decision tree analysis exhibiting possible outcomes after treatment with either uterotonic. PPH, post-partum hemorrhage.

Store of Sarawak General Hospital. The time taken to administer individual drugs and monitoring was estimated from existing internal surveys or time motion analysis previously conducted. The average monthly salary for each grade of staff involved was obtained from the finance unit of the hospital. Because an average salary is estimated based on the grade of a group of staff, no personal identifying information was involved. The staffing cost incurred was then calculated based on the hourly salary and amount of time taken for each procedure described. The type and dosage of additional uterotonic involved in retreatment was drawn from the literature. When discrepancy in the dosage or rate of administration of oxytocin was identified, the majority was used as a reference standard. The cost of blood components and hospitalization was estimated from the 2016 Fee Schedule, Fees Act (Medical) 1951 for Foreigners.

In Malaysia, over half a million babies are born each year in 137 hospitals throughout the country. Fourteen major hospitals contribute data to the National Obstetric Registry and of these, 10 hospitals have delivery rates of more than 8000 per annum. Six of these hospitals have delivery rates exceeding 12 000 per annum.<sup>12</sup> The median number of deliveries per annum in the United Kingdom's National Health Service hospitals or trusts is 4007 (range 1095–14 322 deliveries). Based on this, the authors have arbitrarily defined high volume maternity units as those with more than two times the multiple of median (MoM) or 8000 or more deliveries per annum.<sup>13</sup>

The calculated cost was based on a cohort of 12 000 deliveries with an average cesarean section rate of 25%.<sup>12</sup> The final cost of each arm included the cost of the index medication, additional equipment, medication or investigation and monitoring. The incremental cost effectiveness ratio (ICER) was calculated for PPH. A threshold sensitivity analysis was conducted to ascertain the price that would make carbetocin no longer cost effective in a Malaysian hospital setting. The threshold selected was drawn from a previous local study.<sup>14</sup> All costs are quoted in United States dollars unless otherwise specified.

The Malaysian Research and Ethics Committee approved the study (NMRR ID 16-1620-31495).

## Results

A total of 2012 patients were included from seven randomized controlled trials that fulfilled the inclusion

criteria (Table 1). The trials ranged from 57 to 635 patients who underwent either emergency or elective cesarean sections. Some of the studies specifically excluded patients with placenta previa or abruption but invariably, a proportion of the patients recruited in most studies had risk factors for PPH.<sup>15–17</sup>

The cost of using carbetocin for an estimated 3000 cesarean sections per year in our institution was estimated at \$54 075 more than if oxytocin was used. Based on data extracted from the literature, 600 patients (19.98%) on the carbetocin arm were expected to require retreatment compared to 1055 (35.16%) on the oxytocin arm (Figure S1). The total cost of retreatment amounted to \$20 925.30 and \$25 354.03 for carbetocin and oxytocin, respectively.

The overall proportion of patients with PPH was 14.19% with carbetocin and 17.79% with oxytocin, a mere 3.6% reduction (Table S1). However, in units such as ours, this reduction meant that 108 fewer women would experience PPH after cesarean sections per annum. Patients with PPH would have at least an additional full blood count and require more frequent monitoring, including additional review by the managing team. Thus, the additional cost of managing a single PPH event was \$132.10 (Table 2). From the decision tree analysis, a surplus of \$30 991.91 was required to prevent 108 episodes of PPH when carbetocin was used, thus the ICER for averting an episode of PPH was \$278.70 (Table 3). The threshold sensitivity analysis conducted found that carbetocin ceased to be a cost effective option once the cost reached 1500% more than the base case analysis (Fig. 2). Therefore, the use of carbetocin rather than oxytocin during cesarean section appears cost effective in this respect.

If our cohort of 3000 patients were prophylactically administered carbetocin, 45 patients would require transfusion. With oxytocin, this figure increases to 149 patients. The cost of transfusing a pint of pack cells was \$30 but when the cost of routine monitoring for transfusion reaction and post-transfusion investigation were considered, this would escalate to \$97.46 per patient in our setting (Table S2). Thus, the cost incurred by the provider amounted to \$4385.55 and \$14 521.10 for carbetocin and oxytocin, respectively (Table S3).

## Discussion

A lower risk of retreatment with additional uterotonic was one of the key consistent findings reported when

**Table 1** Characteristics of randomized trials

Study	Carbetocin (patients)	Oxytocin (patients)	Prophylactic oxytocin dose (IU)	PPH risk factors	Cesarean section
Boucher <sup>18</sup>	29	28	32.5	Variable risk	Elective
Dansereau <i>et al.</i> <sup>15</sup>	317	318	25	Variable risk	Elective
Borruto <sup>19</sup>	52	52	10	At least 1 PPH risk factor	Elective & emergency
Attilakos <i>et al.</i> <sup>16</sup>	188	189	5	Variable risk, 25% had at least 1 PPH risk factor	Elective & emergency
El Behery <i>et al.</i> <sup>20</sup>	90	90	20	Obese and nulliparous	Emergency
Razali <i>et al.</i> <sup>17</sup>	276	271	10	50% had PPH risk factors	Emergency
Whigham <i>et al.</i> <sup>21</sup>	59	53	5	Preterm and multiple pregnancy excluded	Emergency

PPH, post-partum hemorrhage.

**Table 2** Cost input for uterotonics and interventions

RESOURCES	COST (US\$)
Cost of carbetocin (vial of 100 mcg)	\$18.20
Cost of oxytocin (vial of 10 IU)	\$0.18
<b>Cost of Retreatment 1</b>	<b>\$11.57</b>
<b>Cost of Retreatment 2</b>	<b>\$233.03</b>
Cost of PPH	\$132.10
Additional blood investigation	\$7.25
Syringe	\$0.07
Needle	\$0.02
Alcohol swabs	\$0.02
Staff time (Investigation)	\$0.72
Additional staff time (management & monitoring)	\$124.02
Cost of Transfusion	\$97.46
Packed cells	\$30.00
IV giving set	\$0.50
Additional blood investigation	\$7.25
Syringe	\$0.07
Needle	\$0.02
Alcohol swabs	\$0.02
Staff time (Investigation)	\$0.72
Additional staff time (management & monitoring)	\$58.88

IV, intravenous.

carbetocin was used in cesarean sections compared to oxytocin.<sup>8</sup> When three additional trials published within the past two years were considered, a statistically

significant reduction in PPH and transfusion were found.<sup>17,20,21</sup> Our unit, which conducts 12 000 deliveries a year with about 3000 cesarean sections, would have to allocate an additional \$54 075 (\$18.20 vs \$0.18) for the use of carbetocin but the potential savings from retreatment, additional staffing, equipment and transfusion meant that the absolute cost increment was \$8.41 more per patient (\$45.39 vs \$36.98).

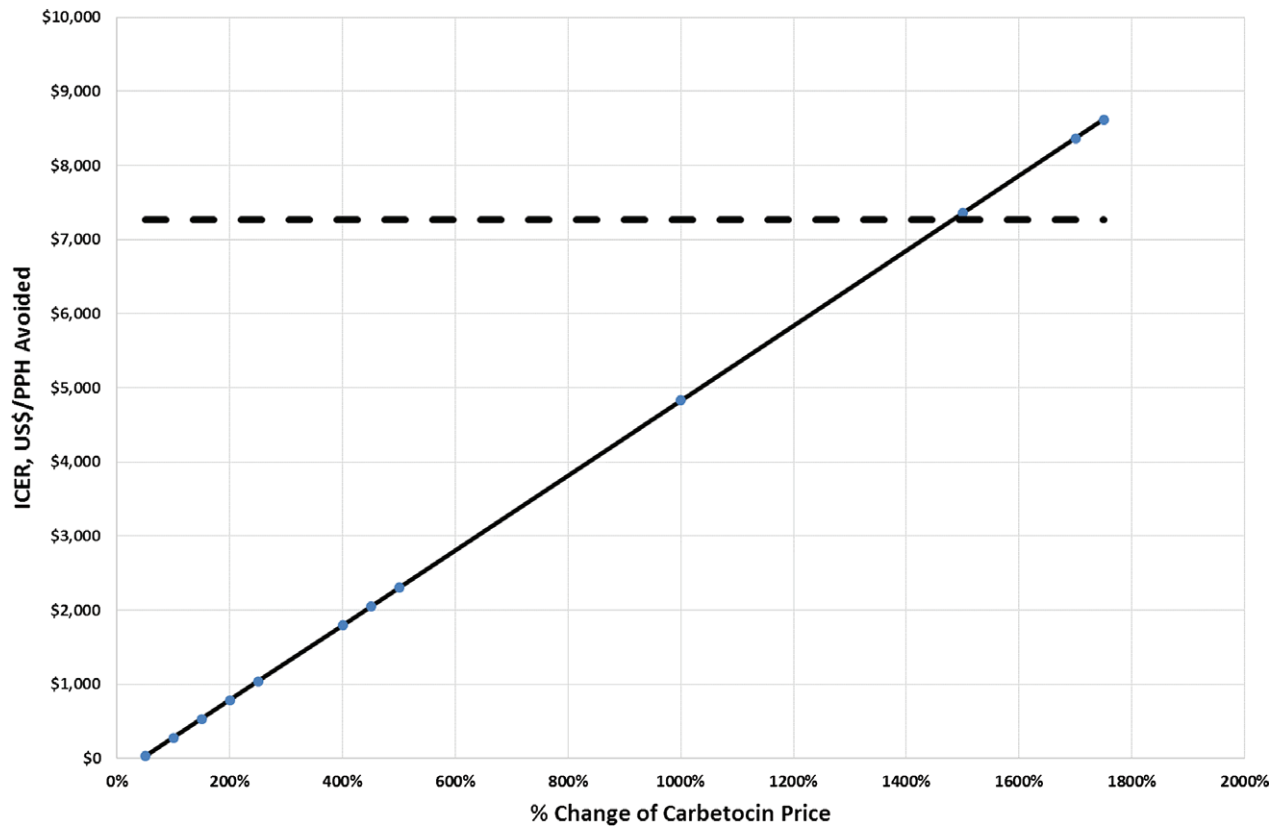
The calculations did not include the cost of prolonged operative time where retreatment was required because a previous trial showed that although most of the additional uterotonics were given intraoperatively they did not increase the total operative time.<sup>17</sup> However, in the same study, the retreatment rate was surprisingly high, at 38.8% for carbetocin and 57.2% for oxytocin. This may reflect a more liberal use of additional uterotonic prophylactically based on surgeons' discretion rather than for therapeutic indications. In contrast, another study showed that more than 50% of women who had blood loss of more than 1000 ml bled outside of theater, consistent with the delayed pattern of hemorrhage commonly exhibited by uterine atony.<sup>21</sup>

Despite the abundance of literature on the clinical effectiveness of carbetocin, there is a paucity of literature on its cost effectiveness. Our findings were

**Table 3** Incremental cost effectiveness ratio of carbetocin versus oxytocin for the prevention of PPH

	Average cost	Average effectiveness	Incremental cost	Incremental effectiveness	ICER
Carbetocin	\$40.10	0.8581	\$10.03	0.036	\$278.70
Oxytocin	\$30.06	0.8221			

ICER, incremental cost effectiveness ratio; PPH, post-partum hemorrhage.



**Figure 2** Threshold sensitivity analysis of carbetocin. The horizontal dotted line represents the threshold below which carbetocin remained cost effective for the prevention of post-partum hemorrhage (PPH). ICER, incremental cost effectiveness ratio.

consistent with Del Angel-García *et al.* who reported a favorable ICER when carbetocin was used in Mexican women with PPH risk factors.<sup>22</sup> In contrast, among low risk women in the setting of a district hospital in the United Kingdom, no economic benefit was found with the use of carbetocin.<sup>23</sup>

The authors recognize the limitations of a cost effectiveness analysis, the problems with estimating the ‘worth’ of human lives and the willingness of policy makers or society to pay for a particular treatment. It also does not measure outcomes such as the cost borne by the patient or health-related quality of life. At least in our setting, in which healthcare provision is heavily subsidized, the former is unremarkable. The authors also recognize that a certain degree of assumption has to be made in the absence of clinical data from randomized trials. Overall, cost effectiveness analysis remains a reasonable approach to evaluate competing therapies.

The efficacy of a uterotonic alone should not be the sole criteria when evaluating treatment; safety, the practicality of administration in units with perpetual relative shortage of staff and adverse effects may limit the value of a drug. In our unit with a high patient turnover, which also doubles as a training center for both junior doctors and nurses alike, the former are pertinent cogitations. Between 2012 and 2016, the labor suite of our unit, which doubled as an obstetric admission center, handled 11 655–12 230 deliveries and between 28 091–29 521 admissions and discharges. With 17 delivery suites available at any one time, the bed occupancy rate was 188–192%, meaning that patients would frequently have to deliver on makeshift beds or additional trolleys. The unit was unable to provide one-to-one midwifery care as it is manned by an average of 46 midwives over three shifts. This meant that at any one time, only 11 out of 17 women received one-to-one care in labor.

A prospective observational study of 10 000 women presenting to an obstetric emergency ward recorded 1976 medication errors, largely from errors with the administration of medications. The wrong dose of oxytocin infusion was highlighted, although it must be clarified that this occurred intrapartum rather than in the context of delivery.<sup>24</sup> Similarities can be drawn though, from the fact that it occurred in an emergency setting and resource-poor environment, as units with high volume deliveries may end up with shortages of staffing and equipment. In a local observational study, the frequency of errors in drug administration was reported to be as high as 8.7%, despite excluding errors that merely involved discrepancy in the timing of administration. Intravenous administration errors were significantly higher than the oral route by almost threefold and one in 10 of the overall errors were deemed to be potentially life threatening.<sup>25</sup>

Avoiding medication error is paramount and embedded within the obstetricians' pillar of training, to ensure *primum non nocere*. Nevertheless, many high volume maternity units also serve as the cradle to nurture junior nursing and medical personnel, resulting in an increased need for supervision, which can be overwhelming for the existing staff. Coupled with an increasingly litigious medical environment and changes in patient expectations, a drug that is simpler to administer and longer acting may prove advantageous. However, the absolute cost of carbetocin can be prohibitive, as the cost of carbetocin is several times higher than oxytocin.

The other salient point to be addressed is the implication of an inadvertent oxytocin dosing error in a post-partum woman and whether it is severe enough to warrant the use of a more costly alternative. Estrogen-modulated oxytocin receptor upregulation occurs in pregnancy, increasing 12-fold at term, compared to the first trimester and almost 80-fold higher than in the non-pregnant state. The sensitivity of oxytocin continues to increase in labor. Large doses of rapidly administered oxytocin produce various adverse effects, such as hypotension, headache, flushing, nausea, vomiting, chest pain, myocardial ischemia, ST-T segment changes, pulmonary edema, severe water intoxication and convulsion.<sup>26</sup>

## Conclusion

In summary, based on the absolute price of the index drug alone, the provider would have reservations

using the more costly uterotonic. However, in terms of pharmacoeconomics, the use of carbetocin resulted in a favorable ICER, especially when the additional outcomes studied were incorporated. The willingness of a unit or institution to fund the longer acting agent would largely depend on the relative values placed on averting retreatment, potential medication error and allocation of human resources.

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## Disclosure

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Figure S1** Probability of retreatment, post-partum hemorrhage or transfusion based on a cesarean rate of 3000 cases per annum.

**Table S1** Effects of interventions from randomized controlled trials involving cesarean deliveries.

**Table S2** Cost breakdown for data input.

**Table S3** Cost per patient.