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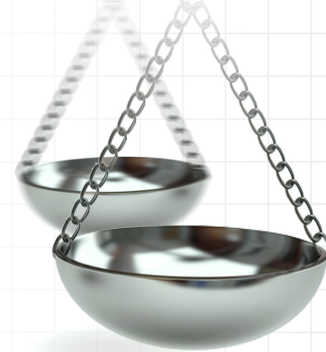
Analysis of the cost-effectiveness of carbetocin for the prevention of hemorrhage following cesarean delivery in Ecuador.

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# Analysis of the cost–effectiveness of carbetocin for the prevention of hemorrhage following cesarean delivery in Ecuador

Journal of **Comparative Effectiveness Research**

**Aim:** To compare the cost of carbetocin with that of oxytocin for the prevention and management of hemorrhage following cesarean delivery in Ecuador. **Materials & methods:** We developed a decision tree based cost–effectiveness model to compare carbetocin with oxytocin in the prevention of hemorrhage following cesarean delivery in Ecuador. Our model was run from a third party payer perspective and was validated by local experts in the field. The efficacy of the interventions was determined based on a systematic review of the literature. Direct costs were calculated based on current National Health Service price lists and retail price. Since the period covered by the analysis was 1 year, costs and health effects were not discounted. **Results:** The difference in costs between the interventions was US\$16.26, with a difference in effectiveness of 0.0067 disability adjusted life years averted. The incremental cost–effectiveness ratio for carbetocin compared with oxytocin for prevention of hemorrhage following cesarean delivery was US\$2432.89 per disability adjusted life year averted. **Conclusion:** Carbetocin is as efficacious and safe as oxytocin for primary prevention of hemorrhage in cesarean delivery in Ecuador. It is highly cost effective for reducing the need for additional uterotonic drugs in both emergency and elective cesarean delivery.

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Postpartum hemorrhage (PPH) is the main cause of maternal death throughout the world [1]. In Ecuador, it is the second most common cause of maternal death after pregnancy-related hypertensive disorders [2]. The most frequent cause of PPH is the inability of the uterus to contract appropriately owing to uterine hypotony or atony. Uterotonic drugs play a key role in the prevention of this condition [3]. Cesarean delivery, whether elective or emergency, is a known risk factor for PPH (odds ratio: 3.4 [95% CI: 3.28–3.95] for emergency cesarean and 2.0 [95% CI: 2.18–2.80] for elective cesarean) [4,5]. The frequency of cesarean delivery has increased significantly in Ecuador during the past

years; on an average 39.2% of all hospital births were by cesarean delivery between 2010 and 2015 (Table 1). Surprisingly the rates of cesarean hysterectomy seem to be extremely high (0.4–3.1 per 100 deliveries) when compared with high-income countries, but this is probably due to the coding errors in the Ecuadorian databases [6].

The options available in Ecuador for pharmacologic management and prevention of PPH include oxytocin, misoprostol, methylergonovine and carbetocin [2]. However, only the first three are on the National Essential Medication List – the definitive list of obligatory medication in the National Health Service – and are financed by the state [8].

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Table 1. Number of live births and hospital discharges after cesarean delivery in Ecuador, 2010–2015.

Diagnosis (ICD-10)	2010	2011	2012	2013	2014	2015
Elective cesarean delivery (O820)	11,061	11,820	10,026	11,665	10,236	13,648
Emergency cesarean delivery (O821)	1817	952	1176	2472	3652	4894
Cesarean hysterectomy (O822)	10,020	8861	8142	1118	4243	4410
Other cesarean delivery (single; O828)	58	247	456	302	128	200
Cesarean delivery, no other specification (O829)	45,569	48,612	47,880	53,352	52,523	41,862
Multiple births, all by cesarean (O842)	326	293	436	415	500	554
Total cesarean deliveries	68,851	70,785	68,116	69,324	71,282	65,568
Total deliveries in hospital facilities (O80–84)	188,400	191,622	179,743	170,237	167,810	161,284
All registered live births (O80–O84)	326,028	332,642	319,227	292,659	284,203	273,280

Data taken from Instituto Nacional de Estadísticas y Censos – INEC, Egresos hospitalarios 2010–2015 [7].

Carbetocin is a long-acting synthetic octapeptide analog of oxytocin with agonist properties. Its clinical and pharmacologic properties are similar to those of natural oxytocin. Compared with oxytocin, carbetocin induces a uterine response that is prolonged in terms of both amplitude and frequency of contractions when administered postpartum [9].

The efficacy of carbetocin has been evaluated by several authors. The studies by Dansereau *et al.* [10], Boucher *et al.* [11], Borruto *et al.* [12], Attilakos *et al.* [13], Reyes and Gonzalez [14], Elgafor El Sharkwy [15] and Fahmy *et al.* [16] and the meta-analyses of Su *et al.* [17] and Jin *et al.* [18] show that the efficacy of carbetocin is comparable to that of oxytocin for the prevention of PPH.

The administration of carbetocin in women who undergo cesarean delivery significantly reduces the need for additional uterotonic agents (RR: 0.64 [95% CI: 0.51–0.81]) and uterine massage (RR: 0.54 [95% CI: 0.31–0.96]) when compared with oxytocin [17]. Carbetocin is also associated with reduced blood loss compared with syntometrine (oxytocin + ergometrine) for prevention of PPH in vaginal delivery and is associated with significantly fewer adverse effects [17]. The systematic review and meta-analysis of Su *et al.* [17] did not reveal a significant increase in the frequency of adverse events after comparing carbetocin with oxytocin. Similarly, after comparing carbetocin with oxytocin in patients with severe pre-eclampsia, Reyes and Gonzalez [14] did not find significant differences in the frequency of adverse events. Elgafor el Sharkwy [15] recorded significantly

less frequent fever and chills in patients who received carbetocin than in patients who received misoprostol and oxytocin. The Society of Obstetricians and Gynecologists of Canada recommends intravenous administration of carbetocin over continuous infusion of oxytocin for prevention of PPH in elective cesarean delivery, since it reduces the need for uterotonic agents [3]. The society also recommends intramuscular carbetocin over continuous infusion of oxytocin during vaginal delivery in women at risk of PPH because it reduces the need for uterine massage to prevent PPH. A large Phase III multinational randomized controlled trial sponsored by the WHO is ongoing to evaluate the noninferiority of room temperature stable carbetocin compared with oxytocin in the prevention of PPH after vaginal birth [19].

Given the increasingly frequent use of carbetocin as the drug of choice for prevention of hemorrhage after cesarean delivery in Ecuador, we compared its cost-effectiveness with that of oxytocin from the perspective of a public third party payer.

## Methods

We performed a decision tree based cost-effectiveness study to compare the use of carbetocin with that of oxytocin for prevention of hemorrhage after cesarean delivery, the probability of using uterine massage and additional uterotonic agents, and the habitual sequence of interventions for control of bleeding resulting from uterine atony (Figure 1). The face validity of the model and the sequence of interventions were confirmed based on interviews with specialists in gynecology

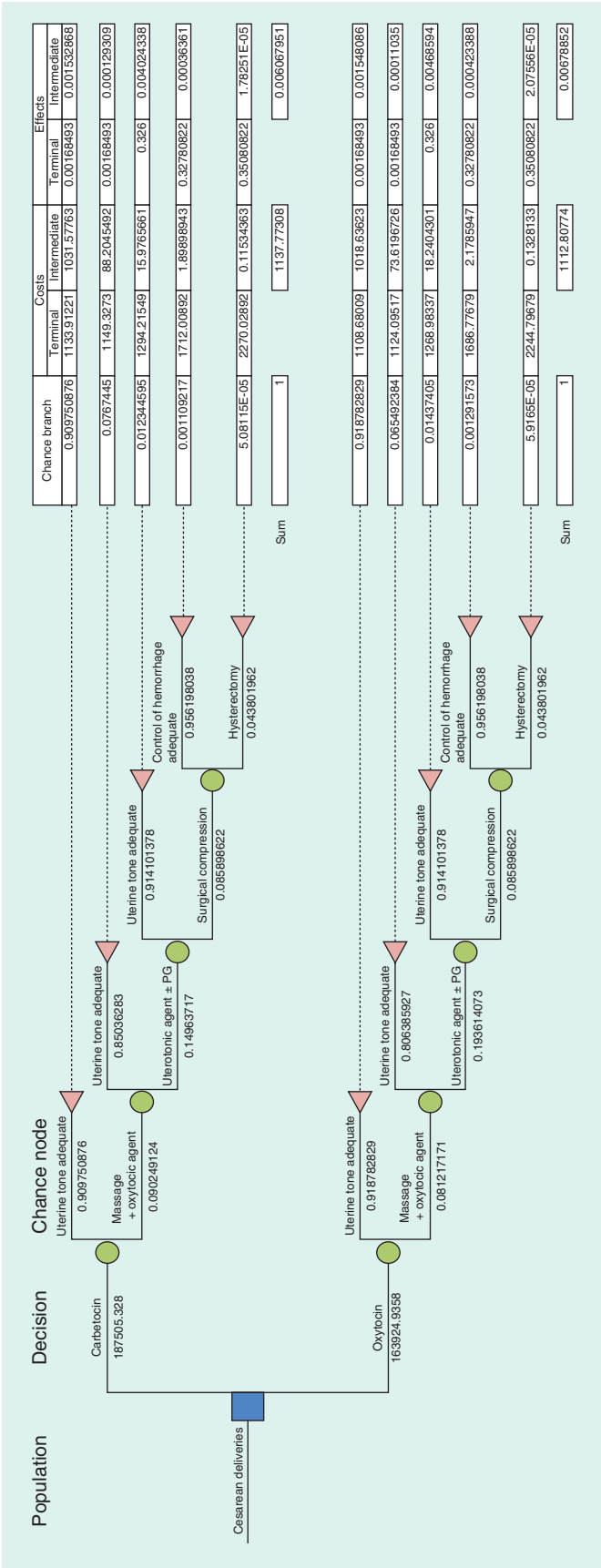


Figure 1. Model for prevention and management of hemorrhage following cesarean delivery.

Table 2. Clinical effectiveness parameters used in the analysis.

Variable	Deterministic		Probabilistic		Study	Ref.
	Base	Range	Distribution	Parameters	First author (year)	
Probability of uterine massage with carbetocin	0.0786	0.0553–0.1106	$\beta$	$\alpha = 29, \beta = 340$	Su <i>et al.</i> (2012)	[17]
Probability of uterine massage with oxytocin	0.1459	0.1136–0.1856	$\beta$	$\alpha = 54, \beta = 316$	Su <i>et al.</i> (2012)	[17]
Probability of additional uterotonic agents with carbetocin	0.1365	0.1111–0.1667	$\beta$	$\alpha = 80, \beta = 506$	Su <i>et al.</i> (2012)	[17]
Probability of additional uterotonic drugs with oxytocin	0.2147	0.1833–0.2497	$\beta$	$\alpha = 126, \beta = 461$	Su <i>et al.</i> (2012)	[17]
Probability of additional uterotonic drugs with ergotamine	0.0874	0.0704–0.108	$\beta$	$\alpha = 76, \beta = 794$	Butwick <i>et al.</i> (2015)	[20]
Probability of additional uterotonic drugs with misoprostol	0.1064	0.0775–0.1444	$\beta$	$\alpha = 35, \beta = 294$	Conde-Agudelo <i>et al.</i> (2013)	[21]
Probability of controlling hemorrhage with uterine compression sutures	0.958	0.798–0.993	$\beta$	$\alpha = 103, \beta = 6$	Matsubara <i>et al.</i> (2013)	[22]
Weight of disability arising from elective cesarean	-0.123	-0.123 to -0.123	–	–	Chatterjee <i>et al.</i> (2015)	[23]
Weight of disability arising from emergency cesarean	-0.326	-0.123 to -0.123	–	–	Chatterjee <i>et al.</i> (2015)	[23]
Weight of disability arising from hysterectomy	-0.349	-0.349–0.349	–	–	WHO (2004)	[24]
Weight of disability arising from anemia	-0.011	-0.011 to -0.011	–	–	WHO (2004)	[24]

and obstetrics from the public and private sectors. The model was constructed using an MS Excel® spreadsheet, which was programmed with macros to run a probabilistic sensitivity analysis with 1000 iterations.

As it is an acute event, the time period for the analysis was 1 year; therefore, costs and health effects were not discounted. The efficacy of interventions to control uterine tone and the weight of the disability associated with cesarean delivery (elective and emergency) complicated by PPH were determined based on the review of the literature (Table 2).

We used a public third party payer perspective, which included only direct costs (human resources, medications, consumables, medical procedures and hospital stay) of the interventions evaluated and their complications (Table 3). The direct costs were determined based on the price list of the National Health System and on retail prices in Ecuador [25]. All prices were in US dollars, which is the official currency in Ecuador. The cost–effectiveness of the interventions was measured as the cost in monetary units of averting one disability adjusted life year (DALY). Cost–effectiveness ratios were calculated, as was the incremental cost–effectiveness ratio, which was defined as the quotient of the difference in costs divided by the

difference in effects [26]. The probabilistic sensitivity analysis was performed using Monte Carlo simulations with 1000 iterations [27]. Following the rules of the WHO’s Commission on Macroeconomics in Health, the intervention under evaluation was considered cost effective if the cost of averting one DALY is equal or below the monetary value of 3 gross domestic products per capita (GDP per capita); and highly cost effective if the cost of averting one DALY was equal or below 1 GDP per capita [28].

## Results

For the base case, the difference in costs between the interventions was US\$16.26, with a difference in effectiveness of 0.0067 DALYs averted (this is the equivalent of gaining approximately 2.4 days of healthy life). The incremental cost–effectiveness ratio for carbetocin compared with oxytocin for prevention of hemorrhage following cesarean delivery was US\$2432.89 per DALY averted. The probabilistic sensitivity analysis revealed the mean (standard deviation) difference in costs to be US\$20.93 (0.29) and the difference in effectiveness to be 0.0066 DALYs averted, with a mean incremental cost–effectiveness ratio of US\$3387.69 per DALY averted (95% CI: US\$3307.18–3468.20).

Parameter	Deterministic (US\$)		Probabilistic (US\$)			Source
	Base	Range	Distribution	Mean	SD	
Cost of one ampoule of carbetocin (100 µg/ml)	25.60	21.39–30.19	γ	25.79	4.40	MSP 2015
Cost of one ampoule of oxytocin (10 IU/ml)	0.15	0.13–0.19	γ	0.16	0.03	MSP 2015
Cost of one ampoule of ergotamine (0.2 mg/ml)	0.65	0.55–0.78	γ	0.67	0.12	MSP 2015
Cost of one misoprostol tablet (200 µg)	0.52	0.44–0.63	γ	0.54	0.10	MSP 2015
Cost per hour of use of an infusion pump	0.03	0.03–0.04	γ	0.03	0.00	Mean retail price
Cost of material for compressive suture (B-Lynch)	6.37	6.37–6.58	γ	6.48	0.11	Mean retail price
Cost of 1000 ml Ringer lactate or saline solution	1.93	1.49–2.37	γ	1.93	0.44	Mean retail price
Cost of 500 ml de Ringer lactate or saline solution	1.29	1.10–1.47	γ	1.29	0.18	Mean retail price
Cost of venoclysis set with vasocan	4.10	3.42–4.78	γ	4.10	0.68	Mean retail price
Cost of each 3- or 5-cc syringe	0.20	0.17–0.23	γ	0.20	0.03	Mean retail price
Cost of cesarean procedure	892.64	892.64–892.64	–	–	–	RPIS 2015 price list
Cost of hysterectomy	1234.99	1234.99–1234.99	–	–	–	RPIS 2015 price list
Cost per minute of physician/ specialist (SP12)	0.36	0.36–0.36	–	–	–	SENRES 2010
Cost per minute of nurse (SP8)	0.23	0.23–0.23	–	–	–	SENRES 2010
Mean cost of daily hospital stay	71.89	71.89–98.42	–	–	–	RPIS 2015 price list

MSP: Ministerio de Salud Pública (*Ministry of Public Health*); RPIS: Red Pública Integral de Salud (*National Health Service*); SD: Standard deviation; SP: Civil service salary scale.

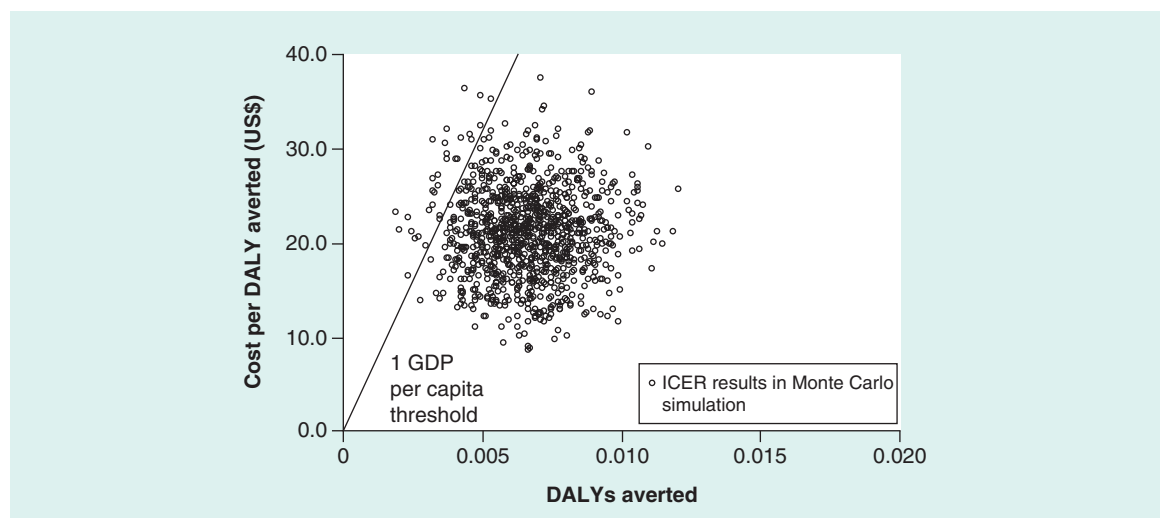
The probabilistic sensitivity analysis (Figure 2) showed that carbetocin was highly cost effective in 97% of the iterations of the Monte Carlo simulations, with an incremental cost-effectiveness ratio below the threshold equal or below 1 GDP per capita (US\$6302 for the year 2015), and in 100% of the simulations, the incremental cost-effectiveness ratio was below the threshold of 3 GDP per capita. Therefore, carbetocin proved to be highly cost effective in Ecuador.

## Discussion

The present study took into account all possible interventions for control of hemorrhage during cesarean delivery, thus increasing the amount of resources used. Nevertheless, carbetocin proved highly cost effective for primary prevention of hemorrhage

during cesarean delivery. Similar studies performed in other countries [29–32] show that administration of carbetocin can reduce costs in the prevention of hemorrhage after cesarean delivery. From these, the prospective cost-effectiveness cohort study conducted by Luni *et al.* [30] is the largest on this topic, and shows in the context of the UK a significant reduction in PPH rates with financial savings.

As with any cost-effectiveness study, the results might not be generalizable to other settings. It is important to note that the present study is subject to limitations of available data in Ecuador. Cesarean rates reported in Ecuador are higher than in other countries, with low quality of coding and reporting of outcomes. Studies with misoprostol conducted in Ecuadorian population suggest the presence of



**Figure 2. Probabilistic sensitivity analysis.** Each dot shows the ICER estimated during Monte Carlo simulations with 1000 iterations. DALY: Disability adjusted life year; GDP: Gross domestic product; ICER: Incremental cost–effectiveness ratio.

genetic polymorphisms that increase adverse reactions like hyperpyrexia and shivering [33,34]. However, the parameters used can be considered as appropriate proxies for the model.

Finally, the large ongoing clinical trials sponsored by WHO can contribute to better estimates of the effectiveness of carbetocin on the prevention of PPH in vaginal deliveries [19]; however, women scheduled for a planned caesarean are not eligible limiting the generalizability of the findings. It is increasingly important

that researchers conducting clinical trials with carbetocin include methods of economic evaluations alongside the trials.

## Conclusion

Carbetocin is as efficacious and safe as oxytocin for primary prevention of hemorrhage after cesarean delivery in Ecuador. It is highly cost effective for reducing the need for additional uterotonic drugs in both emergency and elective cesarean delivery.

## Summary points

- Postpartum hemorrhage is the main cause of maternal death throughout the world.
- Cesarean delivery, whether elective or emergency, is a known risk factor for postpartum hemorrhage.
- Carbetocin induces prolonged and frequent uterine contractions.
- Carbetocin is associated with reduced blood loss.
- Several authors have shown that carbetocin is as efficacious as oxytocin for prevention of postpartum hemorrhage.
- Compared with oxytocin, administration of carbetocin in cesarean delivery significantly reduces the need for additional uterotonic agents and uterine massage.
- Carbetocin is increasingly used as the drug of choice for the prevention of hemorrhage after cesarean delivery in Ecuador.
- Based on official data, carbetocin proved to be highly cost effective for primary prevention of hemorrhage during cesarean delivery in Ecuador.

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## Author contributions

A Henríquez-Trujillo conceived, developed and analyzed the economic evaluation model. R Lucio-Romero and

K Bermúdez-Gallegos collected and analyzed epidemiological and cost information. A Henríquez-Trujillo, K Bermúdez-Gallegos and R Lucio-Romero drafted and revised the final version of the article.

## Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial



interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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## Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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