Cost-effectiveness of Carbetocin versus Oxytocin for Prevention of Postpartum Hemorrhage Resulting from Uterine Atony in Women at high-risk for bleeding in Colombia

Rendimento da carbetocina versus oxitocina para a prevenção da hemorragia pós-parto resultante da atonia uterina em mulheres com alto risco de sangramento na Colômbia

Yaneth Gil-Rojas[1] Pieralessandro Lasalvia[1] Fabián Hernández[1] Camilo Castañeda-Cardona[1] Diego Rosselli[2]

[1] NeuroEconomix, Bogota, Colombia
[2] Department of Clinical Epidemiology and Biostatistics, Facultad de Medicina de la Pontificia Universidad Javeriana, Bogota, Colombia

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Address for correspondence Diego Rosselli, Department of Clinical Epidemiology and Biostatistics, Facultad de Medicina de La Pontificia Universidad Javeriana, Carrera 7 No. 40–62, Bogota, Colombia (e-mail: diego.rosselli@gmail.com).

Abstract

Objective To assess the cost-effectiveness of carbetocin versus oxytocin for prevention of postpartum hemorrhage (PPH) due to uterine atony after vaginal delivery/cesarean section in women with risk factors for bleeding.

Methods A decision tree was developed for vaginal delivery and another one for cesarean, in which a sequential analysis of the results was obtained with the use of carbetocin and oxytocin for prevention of PPH and related consequences. A third-party payer perspective was used; only direct medical costs were considered. Incremental costs and effectiveness in terms of quality-adjusted life years (QALYs) were evaluated for a one-year time horizon. The costs were expressed in 2016 Colombian pesos (1 USD = 3,051 Col$).

Results In the vaginal delivery model, the average cost of care for a patient receiving prophylaxis with uterotonic agents was Col$ 347,750 with carbetocin and Col$ 262,491 with oxytocin, while the QALYs were 0.9980 and 0.9979, respectively. The incremental cost-effectiveness ratio is above the cost-effectiveness threshold adopted by Colombia. In the model developed for cesarean section, the average cost of a patient receiving prophylaxis with uterotonics was Col$ 461,750 with carbetocin, and Col$ 481,866 with oxytocin, and the QALYs were 0.9959 and 0.9926, respectively. Carbetocin has lower cost and is more effective, with a saving of Col$ 94,887 per avoided hemorrhagic event.

Conclusion In case of elective cesarean delivery, carbetocin is a dominant alternative in the prevention of PPH compared with oxytocin; however, it presents higher costs than oxytocin, with similar effectiveness, in cases of vaginal delivery.

Keywords
- cost-effectiveness
- carbetocin
- oxytocin
- prevention postpartum hemorrhage
- pregnancy
- high-risk

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Resumo

Objetivo Avaliar a relação custo-eficácia da carbetocina versus oxitocina para prevenção de hemorragia pós-parto (HPP) vaginal e cesariana devido à atonia uterina em mulheres com fatores de risco para desenvolver sangramento.

Métodos Foram desenvolvidos protocolos de manejo para parto vaginal e outra para parto por cesárea e analisados resultados obtidos com carbetocina e oxitocina na prevenção de HPP, assim como, consequências relacionadas à ocorrência do evento hemorrágico. A perspectiva utilizada foi a do terceiro pagador, portanto, apenas os custos médicos diretos foram levados em consideração. Os custos incrementais e a eficácia em termos de anos de vida ajustados pela qualidade (QALY) foram avaliados para um horizonte de tempo de um ano. Os custos foram expressos em pesos colombianos de 2016 (1 USD = 3.051 Col$).

Resultados No modelo de parto vaginal, o custo médio de cuidados para um paciente que recebeu profilaxia com agentes uterotônicos foi de Col$ 347.750 com carbetocina e Col$ 262.491 com oxitocina, enquanto os QALYs foram 0,9980 e 0,9979, respectivamente. O índice incremental de custo-efetividade está acima do limite de custo-efetividade adotado pela Colômbia. No modelo desenvolvido para parto por cesárea, o custo médio do paciente que recebeu profilaxia com terapia uterotônica foi de Col$ 461.750 com carbetocina e Col$ 481.866 com oxitocina e os QALYs foram 0,9959 e 0,9926, respectivamente. A carbetocina foi a alternativa com menor custo e maior efetividade com uma economia de $94.887 por evento hemorrágico evitado.

Conclusão A carbetocina no parto eletivo por cesárea é uma alternativa dominante na prevenção da PPH em relação à oxitocina; porém representa custos mais altos com uma eficácia similar à da oxitocina no caso de parto vaginal.

Palavras chave

- análise custo-eficiência
- carbetocina
- oxitocina
- prevenção
- hemorragia pós-parto
- gravidez de alto risco

Introduction

Postpartum hemorrhage (PPH) is defined as a blood loss greater than 500 mL within 24 hours postpartum and is considered severe if the loss reaches 1,000 mL in the same time interval.[1] Postpartum hemorrhage affects ~ 2% of women in labor and it is responsible a quarter of maternal deaths. Uterine atony is the most common cause of this condition, but there may be others, such as genital trauma, uterine rupture, placental retention or maternal clotting disorders. The methods of active behavior during delivery, which include administration of prophylactic uterotonics after the birth of the newborn, early clamping and cutting of the umbilical cord, controlled traction of the cord, and uterine massage, have been associated with a considerable reduction in the frequency of PPH.[1]

Colombia has made progress in reducing maternal mortality by 25%; however, there are still ~ 400 deaths per year associated with pregnancy and delivery.[2] During 2012, when surveillance for the event of extreme maternal morbidity was initiated, hemorrhagic complications ranked second, with 23.1%. In 2013, 2014, 2015 and 2016, the proportions of cases of extreme maternal morbidity attributed to hemorrhagic complications were 20%, 20.2%, 18% and 14.5%, respectively.[3] Likewise, there has been a decline in the proportion of maternal deaths attributed to bleeding complications, reaching 13% in 2016.[3] These values show the impact of active behavior applied in the local context in reducing maternal morbidity and mortality attributed to PPH.

Uterotonic agents for prevention of PPH include oxytocin, methylergonovine, misoprostol and, more recently, carbetocin. Oxytocin is the most frequently used agent but, due to its short half-life, it must be administered by intravenous infusion for sustained uterotonic activity. Carbetocin has an efficacy and safety profile very similar to oxytocin and, due to its pharmacokinetic characteristics, has a longer uterotonic activity.[4–6] According to the national guidelines, oxytocin is the uterotonic agent of choice in prevention; however, international guidelines like those from the Royal College of Obstetricians and Gynaecologists (RCOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) already include carbetocin as an alternative, mainly in elective caesarean section.[4–6]

The objective of this evaluation was to estimate the incremental cost-effectiveness ratio of carbetocin compared with oxytocin for prevention of PPH by uterine atony in women with at least one risk factor for hemorrhage, from the perspective of the Colombian health system. Women with low risk for hemorrhage were not considered, since the indication for them is less clear. The study was based on the guidelines established in the manual for the elaboration of economic assessments in health proposed by the national Institute of Technology Assessment in Health (IETS).[7]

Methods

A cost-effectiveness analysis was developed from the perspective of the third-party payer to compare the use of carbetocin in the prevention of PPH with that of oxytocin in women with the presence of at least one risk factor for hemorrhage due to uterine atony. Among the risk factors described for PPH due to uterine atony are: multiple gestation, polyhydramnios, macrosomia, large multiparous, severe hydrocephalus, prolonged labor and chorioamnionitis.[8] A model for vaginal delivery and another one for cesarean delivery are presented separately because the characteristics of these populations may change, as well as risk factors and response to interventions. The main outcome was prevention of PPH, defined as a blood loss exceeding 500 mL.[9] Also, as part of the sequential analysis, the consequences of the hemorrhagic event with each of the alternatives were considered, particularly the treatment of PPH, use of additional uterotonics and the requirement of surgical intervention. Considering that there are several outcomes that measure the effectiveness of treatment (prevention of PPH, use of additional uterotonics, adverse events), quality-adjusted life years (QALYs) were used as a common outcome.[7] The time horizon considered in the economic evaluation was 1 year, so no discount rate was required.

Decision Model

The models were constructed from the review of previous studies,[10–14] and were discussed and validated by a group of thematic experts. Two decision trees were developed with TreeAge Pro Suite 2009 (TreeAge Software Inc., Williamstown, MA, USA), one for cesarean section (►**Fig. 1**) and one for vaginal delivery (►**Fig. 2**). The model begins with women with the presence of at least one risk factor for PPH due to uterine atony who can receive prophylaxis with any of the technologies being evaluated: carbetocin or oxytocin. The first branch defines the occurrence or not of PPH (blood loss > 500 mL), which corresponds to an analysis of the response to preventive interventions. Carbetocin is available as an injectable solution of 100 mcg/mL and is a drug for hospital use that should be administered in a single dose of 100 mcg in both vaginal and cesarean deliveries. Oxytocin is available in an injectable solution of 5 IU/mL or 10 IU/mL, and the recommended dose in cases of vaginal delivery is 5 to 10 IU, intramuscularly, but in case of cesarean section, an IV bolus of 5 IU is recommended followed by an infusion of 30 IU.

Subsequently, sequential events that take place in the event of PPH occur until survival or death at hospital discharge and whether or not the recommended treatments are

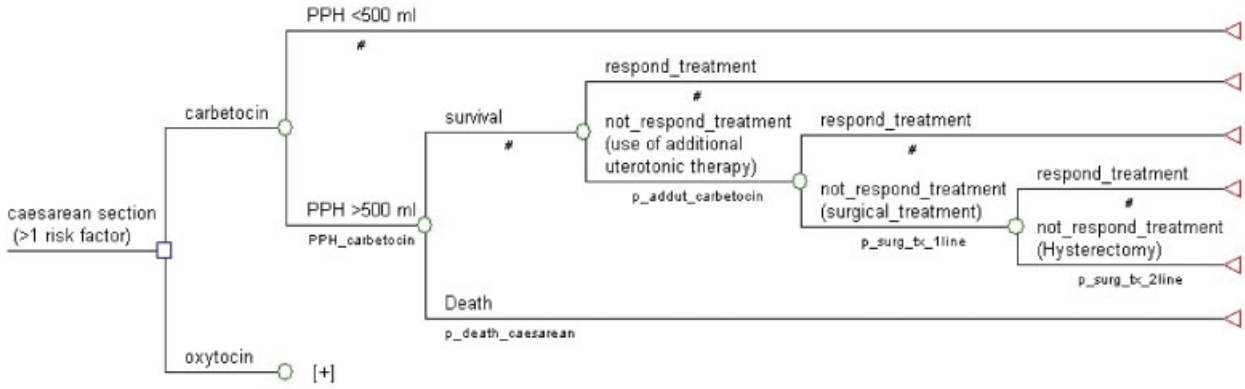

Fig. 1 Decision model in the analysis of PPH in cesarean section.

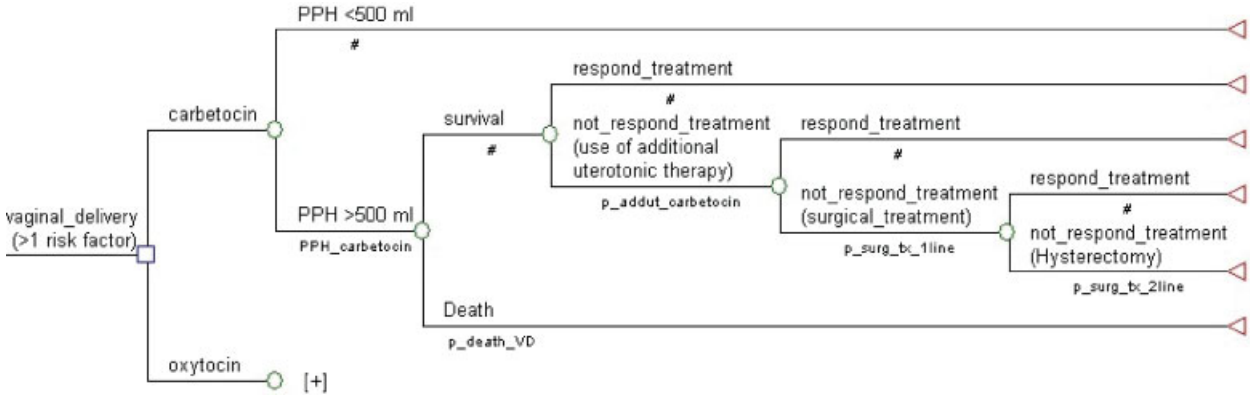

Fig. 2 Decision model in the analysis of PPH in vaginal delivery.

given. If PPH is present, the patient is given a first line of treatment, and if no response is obtained, additional uterotonics are administered; if no response to the pharmacological treatment is obtained, a first surgical approach including uterine tamponade and/or hemostatic suture is performed. If the patient does not respond to this treatment, a second-line surgical procedure would be performed, which usually corresponds to hysterectomy.

Costs

Due to the perspective considered, only direct medical costs required to prevent and treat hemorrhagic events with each of the alternatives were taken into account. All costs were expressed in Colombian pesos in 2016. The resource identification was based on the information from clinical practice guidelines and that provided by a group of clinical experts.

We considered laboratories, procedures and hospital stay required in the process of care of a patient from the administration of carbetocin or oxytocin. If no PPH was present, the costs of the drugs administered in prevention and the hospital stay after vaginal delivery and cesarean section were considered. If the event was present, the costs of first and second line pharmacological treatments, and first and second line surgical approaches were considered. To obtain the cost of medications, the following sources were consulted: 2016 Report of the Drug Price Information System (SISMED)[7] and official documents of price regulation for medicines issued by the Ministry of Health.[15] The average price reported for a carbetocin ampoule of 100 mcg was Col$ 95,800 and that of the oxytocin ampoule of 10 IU was Col$ 1,130. The calculation of costs for procedures associated in particular with the treatment follow-up was performed with the Social Security Institute (ISS, in the Spanish acronym) Fee Manual (Agreement 256 of 2001), with a 30% increase for the case base scenario.[16] The prices of medical supplies, particularly surgical material, were obtained from the "Colombia Efficient Acquisition" (Secop I, in the Spanish acronym) portal.[17]

Only the most frequently reported adverse events for carbetocin and oxytocin, which are nausea and vomiting, were considered in the model. The identification of resources required for the management of adverse reactions was performed with the assistance of a clinical expert. The costs of adverse events were included within the treatment costs, weighted by the frequency of presentation. The total costs in vaginal and cesarean deliveries for the compared alternatives are presented in ►**Tables 1** and **2**, respectively.

Effects

The model parameters were obtained from randomized clinical trials comparing carbetocin with oxytocin, from local databases and expert consultation. The studies considered were identified from a panoramic review developed to evaluate the effectiveness and safety of carbetocin compared with other oxytocics in the prevention of PPH.

To obtain information on mortality in patients with PPH, several sources were consulted: the Individual Health Service Provision Registry (RIPS, in the Spanish acronym),[18] vital statistics of National Administrative Department of Statistics (DANE, in the Spanish acronym),[19] the National Public Health

Table 1 Total costs in the vaginal delivery model (base case)

Group of patients	Carbetocin	Oxytocin
No PPH	$ 183,245	$ 89,442
PPH responding to the 1st line of pharmacological treatment	$ 1,426.303	$ 1,332.499
PPH that respond to additional uterotonics	$ 109,843	$ 16,040
PPH that respond to the first surgical approach	$ 472,038	$ 1,332.499
PPH responding to hysterectomy	$ 1,310.406	$ 1,216.603
Death	$ 231,494	$ 137,691

Abbreviation: PPH, postpartum hemorrhage.

Table 2 Total costs in the cesarean model (base case)

Group of patients	Carbetocin	Oxytocin
No PPH	$ 271,727	$ 177,134
PPH responding to the 1st line of pharmacological treatment	$ 1,427.365	$ 1,332.772
PPH that respond to additional uterotonics	$ 110,906	$ 16,613
PPH that respond to the first surgical approach	$ 964,178	$ 869,585
PPH responding to hysterectomy	$ 1,311.469	$ 1,216.876
Death	$ 231,468	$ 136,798

Abbreviation: PPH, postpartum hemorrhage.

Surveillance System (SIVIGILA, in the Spanish acronym)[3] and the published literature. Consultation in RIPS and vital statistics was performed using the following diagnostic codes: O700, O701, O702, O703, O709, O712, O713, O714, O719, O720, O721, O730, O731, O900, O901, O902, O723, O622 years O621. For the baseline scenario, the mortality data for hemorrhagic complications were taken from SIVIGILA, and a sensitivity analysis was performed considering a minimum of 0% and a maximum of 3.1% as reported in the study by Sheldon et al.[20]

The quality-of-life (utility) weights were obtained through a search in the cost-effectiveness analysis (CEA) Registry of Tufts University. Baseline utilities are those related to vaginal and cesarean deliveries. From these, there is a decrease in the quality of life in the population that presents PPH, either because of the requirement of transfusions or because of the need for surgical interventions. The parameters considered in the models are presented in ►**Table 3**.

Cost-effectiveness

The incremental cost was calculated as the difference between the costs, and the incremental effectiveness as the difference between QALYs obtained when comparing the alternatives. Incremental cost and incremental effectiveness were used to calculate the incremental cost-effectiveness ratio (ICER): The ICER was compared with a cost-effectiveness threshold of 1 gross domestic product (GDP) per capita and 3 GDP per capita. The intervention is considered "cost-effective" if the ICER is below 1 GDP per capita and as "potentially cost-effective" if it is less than 3 times GDP per capita

Sensitivity Analysis

A deterministic and a probabilistic sensitivity analyses were performed, the latter using Monte Carlo simulations.

Results

Model for Caesarean Section

The cost-effectiveness ratio of carbetocin compared with oxytocin is presented in ►**Table 4**. Carbetocin is the most effective treatment, and it is less expensive compared with oxytocin, making it the dominant alternative. When considering the outcome of PPH incidence, it is observed that for each hemorrhagic event avoided with the use of carbetocin Col$ 94,887 are saved.

According to the deterministic sensitivity analysis, at the proposed intervals, the variable that can impact the ICER, so that it is below the threshold, is the proportion of patients presenting with hemorrhagic events with each of the alternatives. Since this variable corresponds to a measure of drug effectiveness, it will not vary significantly until new and more robust evidence is available.

A probabilistic sensitivity analysis was performed with the probability distributions related to the methodology for each of the variables and a Monte Carlo simulation was performed with 1,000 iterations to evaluate the consistency of the results (►**Fig. 3**). A willingness to pay threshold of Col$ 53,090.188 (3 times the per capita GDP of Col$ 17,696.729) was established. In all cases, carbetocin was taken as baseline and oxytocin as a comparator. In 52% of the iterations carbetocin is maintained as a dominant alternative since it is more effective and less costly. In 16.4% of the iterations carbetocin is dominated by oxytocin. In 16.3%, it is more expensive and more effective, but it is above the willingness to pay threshold, while in 15.3%, it is below the threshold.

The acceptability curve (►**Fig. 4**) shows that carbetocin proves to be a cost-effective alternative in 70% of the simulations considering a threshold of 3 GDP/per capita (Col$ 53,090.188).

Model for Vaginal Delivery

The cost-effectiveness ratio of carbetocin compared with oxytocin is presented in ►**Table 5**. Carbetocin is the most effective treatment, but it is also costlier compared with oxytocin. The difference in terms of QALYs and incidence of PPH is small between the two treatments. The ICER is above the cost-effectiveness threshold adopted by Colombia, and when considering the outcome of PPH incidence it is observed that the cost required to avoid additional hemorrhagic events is high.

According to the univariate sensitivity analysis, the variables that can impact the ICER are the proportion of patients presenting with bleeding events in each group as well as the cost of carbetocin.

A probabilistic sensitivity analysis was performed considering the costs and other variables that could become a source of heterogeneity. The probability distributions related in the methodology for each of the variables were taken into account, and a Monte Carlo simulation was performed with 1,000 iterations to evaluate the consistency of the results. The threshold, again, was Col$ 53,090.188. ►**Fig. 5** presents the Monte Carlo simulation for incremental analysis. In all cases, carbetocin was taken as the comparator and oxytocin as the baseline. It is observed that in 46.8% of the iterations, oxytocin remains a dominant alternative since it is more effective and less costly. In 27% of iterations carbetocin is the dominant alternative. In 18.9% of the iterations carbetocin is more effective and more expensive than oxytocin but is above the willingness to pay, while at 7.3% it is below the willingness to pay.

According to the acceptability curve, only carbetocin appears as a cost-effective alternative in 30% of the simulations considering a threshold of 3 times per capita GDP but it does not substantially increase its likelihood of being cost-effective, even with a willingness to pay of Col$ 200,000.000.

Discussion

The results obtained are consistent with those found in other studies. According to the evaluation developed by Moosivand et al,[14] from the perspective of Iran's health system and society, carbetocin is a dominant alternative compared with

Table 3 Model parameters

Parameter	Base	Min	Max	Distribution	Source
Vaginal delivery					
RR PPH carbetocin	0.950	0.430	2.090		Boucher et al. (2004)[21]
Probability of PPH in oxytocin group	0.164	0.074	0.361	Beta	Boucher et al. (2004)[21]
Probability of PPH in carbetocin group	0.156	0.071	0.343	Beta	Calculated
Probability of death by hemorrhagic event	0.003	0.000	0.031	Beta	INS[3] Sheldon et al. (2014)[20]
RR use of additional uterotonics carbetocin	0.930	0.440	1.940		Boucher et al. (2004)[21]
Probability use of additional uterotonics oxytocin	0.156	0.074	0.325	Beta	Boucher et al. (2004)[21]
Probability use of additional uterotonics carbetocin	0.145	0.069	0.302	Beta	Calculated
Caesarean section					
RR PPH carbetocin	0.520	0.290	0.930		Borruto et al. (2009)[22]
Probability of PPH in oxytocin group	0.442	0.247	0.791	Beta	Borruto et al. (2009)[22]
Probability of PPH in carbetocin group	0.230	0.128	0.411	Beta	Calculated
Probability of death by hemorrhagic event	0.008	0.000	0.031	Beta	INS[3] Sheldon et al. (2014)[20]
RR use of additional uterotonics carbetocin	0.700	0.510	0.980		Borruto et al. (2009)[22] Attilakos et al. (2010)[23]
Probability use of additional uterotonics oxytocin	0.374	0.272	0.524	Beta	Borruto et al. (2009)[22] Attilakos et al. (2010)[23]
Probability use of additional uterotonics carbetocin	0.262	0.191	0.367	Beta	Calculated
Vaginal and cesarean delivery					
Requirement for first-line surgical intervention (tamponade and hemostatic suture)	0.100	0.000	0.120	Beta	Experts
Requirement for second line surgical intervention (hysterectomy)	0.010	0.000	0.050	Beta	Experts
Surgical approach					
Proportion of patients undergoing uterine tamponade	0.60				Experts
Proportion of patients undergoing hemostatic suture	0.40				Experts
Frequency of complications of uterine tamponade					
Infection	0.02				Experts
Frequency of complications of hemostatic suture B-Lynch					
Ureteral injury	0.002				Experts
Bladder injury	0.001				Experts
Intestinal injury	0.001				Experts

(*Continued*)

Table 3 (*Continued*)

Parameter	Base	Min	Max	Distribution	Source
Frequency of hysterectomy complications					
Infection	0.02				Experts
Ureteral injury	0.01				Experts
Bladder injury	0.01				Experts
Intestinal injury	0.005				Experts
Utilities					
Vaginal delivery utility (Non-PPH)	0.9997	0.9996	0.9998	Triangular	24
Caesarean section utility (No PPH)	0.9996	0.9995	0.9997	Triangular	24
PPH (First Line Treatment) Utility - vaginal delivery	0.9918	0.9913	0.9922	Triangular	25
PPH (First Line Treatment) Utility - Caesarean section	0.9917	0.9912	0.9921	Triangular	25
Disutility by endometritis	0.0144	0.0132	0.0155	Triangular	25
Disutility due to operative injury	0.0303	0.0280	0.0326	Triangular	25
Hysterectomy disutility	0.0334	0.0306	0.0363	Triangular	25

Abbreviation: PPH, postpartum hemorrhage; RR, risk ratio; RR PPH, risk ratio of postpartum hemorrhage.

Table 4 Results of the base case

Cost-utility					
	QALY	**Cost**	**ΔQALY**	**Δ Cost**	**ICER ($/QALY)**
Carbetocin	0.9959	$ 461.750	0.00337	($ 20,116)	Dominant
Oxytocin	0.9926	$ 481.866			
Cost-effectiveness					
	Incidence PPH	**Cost**	**Avoided events**	**Δ Cost**	**ICER ($/Avoided PPH)**
Carbetocin	0.230	$ 461,750	0.212	($ 20,116)	($ 94,887)
Oxytocin	0.442	$ 481,866			

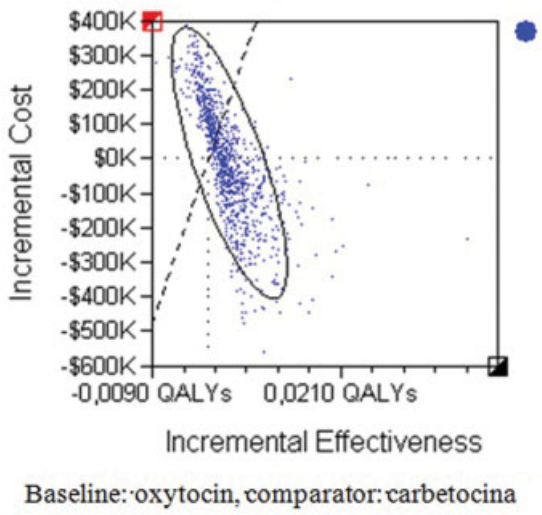

Fig. 3 Monte Carlo simulations in the cost-effectiveness incremental plane.

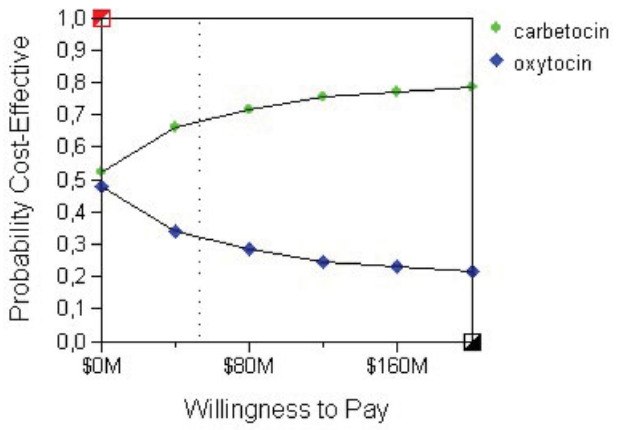

Fig. 4 Acceptability curves.

Table 5 Results of the base case

Cost-utility					
	QALY	Cost	Δ QALY	Δ Cost	ICER ($/QALY)
Carbetocin	0.99800	$ 347,750	0.00009	$ 85,259	$974,790.719
Oxytocin	0.99791	$ 262,491			
Cost-effectiveness					
	Incidence PPH	Cost	Avoided events	Δ Cost	ICER ($/Avoided PPH)
Carbetocin	0.156	$ 347,750	0.008	$ 85,259	$ 10,657.375
Oxytocin	0.164	$ 262,491			

Abbreviations: ICER, incremental cost-effectiveness ratio; PPH, postpartum hemorrhage; QUALY, quality-adjusted life year.

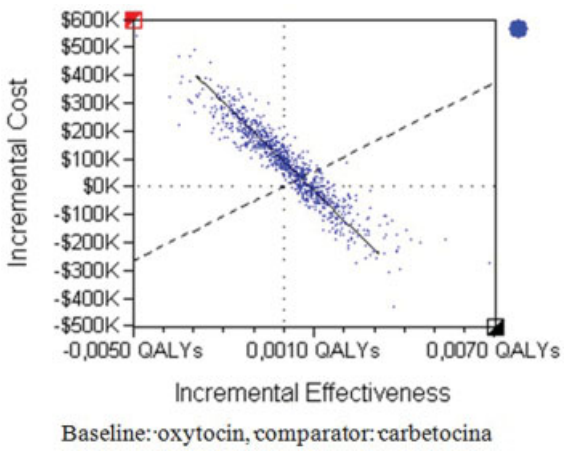

Fig. 5 Monte Carlo simulations in the cost-effectiveness incremental plane.

oxytocin, considering the best possible scenarios (maximum oxytocin price); however, is not cost-effective in other scenarios. In the probabilistic sensitivity analysis, 51.7% of the iterations were below the willingness to pay threshold for QALY.

In the model of women with at least one risk factor for PPH during vaginal delivery, carbetocin is more effective than oxytocin; however, from the point of view of health system and willingness to pay in the country, it is not a cost-effective alternative. The difference in costs between alternatives is close to Col$ 80,000 but the difference in terms of QALY is small. According to the literature review, no studies were identified in vaginal delivery, which may be related in part to the fact that carbetocin does not appear as a recommendation of choice in the prevention of PPH due to uterine atony after vaginal delivery.[1,4–6,9]

The limitations of this study are related to the assumptions applied and the lack of studies performed in the high-risk population, both in patients undergoing vaginal delivery and cesarean delivery. The risk of hemorrhage and the use of additional uterotonics differs from one study to the other, in part because of different oxytocin dosing. We used the dosing scheme (and the PPH risk) described by Borruto et al[22] and Attilakos et al[23] because they included women with at least one risk factor for PPH. In other studies, using even higher doses of oxytocin,[26–29] the risk reduction with carbetocin was even greater; however, there are differences in the characteristics of the population, particularly related to the level of risk that does not allow to clearly observe the differences between alternatives, so it was preferred to adopt a conservative scenario. Regarding utility values, these were based on international studies, since there are no quality of life studies available in our country, and these may not necessarily reflect the preferences of Colombian patients. In addition, in certain cases, the utility levels referred to in the literature were obtained from a group of experts, so the estimated values may not correspond to real life.

The costing of the different health states and events of the model was performed with the help of clinical experts through the development of a typical case, since there are restrictions to access databases with this type of information and considering that the group of experts is small the estimated resources may not necessarily correspond to those used in the country.

Conclusion

In this study, the economic model developed for cesarean section shows that carbetocin has greater effectiveness and lower costs, making it a dominant alternative for the prevention of PPH in high-risk patients. Sensitivity analyses show that within the price range reported in SISMED, it remains either as a dominant alternative, or is below the willingness to pay threshold. The economic model developed for vaginal delivery shows that carbetocin has a cost per additional QALY higher than the acceptable threshold for Colombia.

Contributions

Gil-Rojas Y., Hernández F., Lasalvia P., Castañeda-Cardona C. and Rosselli D. contributed with the design, data collection, analysis and interpretation of the information, preparation of the preliminary publication, critical review and final approval of the version to be published.

Conflicts of Interest
This study was funded by Biopas Laboratories of Colombia. The authors declare that they have no other conflicts of interest.

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