Research Article

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Pharmacoeconomic study comparing carbetocin with oxytocin for the prevention of hemorrhage following cesarean delivery in Lima, Peru

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Postpartum hemorrhage is one of the main causes of maternal death. Oxytocin has traditionally been used to prevent postpartum hemorrhage. **Aim:** To compare oxytocin with carbetocin, a long-acting analog of oxytocin, for prevention of uterine hemorrhage after cesarean delivery. **Materials & methods:** Clinical data were retrieved from the 2012 Cochrane meta-analysis *"Carbetocin for preventing postpartum hemorrhage"*. A decision tree was constructed. The direct costs were those of medications from the Peruvian official price list (DIGEMID). Costs associated with additional oxytocic drugs, blood transfusions, postpartum hemorrhage kits and hysterectomy were obtained from Hospital Nacional Edgardo Rebagliati Martins. The perspective of the study was that of the payer. The time horizon for calculating quality-adjusted life years (QALYs) was 1 year (2015). **Results:** Patients who received carbetocin required fewer additional uterotonic agents, had fewer hemorrhages and received fewer blood transfusions. Therefore, the costs associated with these interventions were lower. The incremental cost–effectiveness ratio was S/. 49,918 per QALY gained, which is lower than the threshold we estimated for Peru. **Conclusion:** Carbetocin is more cost-effective than oxytocin for prevention of uterine hemorrhage after cesarean delivery.

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Keywords: carbetocin • pharmacoeconomic study • postpartum hemorrhage

Postpartum hemorrhage is one of the main causes of maternal mortality in both developed and developing countries. According to WHO, approximately 800 women per-day die of complications associated with pregnancy or childbirth throughout the world. Similarly, severe postpartum hemorrhage is reported in around 11% of livebirths [1].

In 2015, a total of 414 maternal deaths were reported in Peru; of these, approximately 42% were due to hemorrhage [2]. During 2014, The Peruvian National Health System (ESSALUD) recorded 49 maternal deaths, that is, 11% of all maternal deaths in the country. In the ESSALUD, uterine hemorrhage is the third cause of maternal death, occurring in 10% of all births (4% for vaginal delivery and 6% for cesarean delivery) [3].

The risk of postpartum hemorrhage is much greater in cesarean delivery, especially in developing countries, where most operations are performed as emergency procedures [4]. In most cases, excessive bleeding during or after childbirth is caused by uterine atony [5]. Women are also exposed to the risks arising from massive blood transfusions and radical surgical procedures such as hysterectomy [6].

Several systematic reviews have shown that prophylaxis with uterotonic agents significantly reduces the risk of postpartum hemorrhage [7]. The most commonly studied and widely used drug for this purpose is oxytocin; in fact, the WHO recommends oxytocin for management of the third stage of labor [8]. Pharmacological management of postpartum hemorrhage has been studied for several years, and one of the options considered is carbetocin, an

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oxytocin agonist. Carbetocin is a long-acting synthetic analog of oxytocin with a half-life of 40 min. After 2 min of intravenous administration, it can induce tetanic uterine contractions that last for 6 min [9,10].

A 2004 study found that 100 μg of intramuscular carbetocin was as effective as 10 units of oxytocin and reduced the need for uterotonic interventions [11]. Since then, there have been some clinical studies comparing the effectiveness of carbetocin and oxitocyn in preventing postpartum hemorrhage [12,13–15].

In 2012, data from these studies were pooled to determine a general effect of treatment in a meta-analysis with the aim of knowing whether carbetocin was as efficacious as conventional uterotonic agents for the prevention of postpartum hemorrhage (PPH). A systematic review of the literature on this field and a meta-analysis were performed to evaluate the efficacy and safety profile of carbetocin for prevention of PPH. Current evidence shows that compared with oxytocin, carbetocin significantly reduces the need for additional uterotonic agents and uterine massage in women undergoing cesarean delivery [16].

Once the efficacy and safety profile of an alternative has been demonstrated, efficiency must be assessed in terms of costs and benefits in order to optimize the use of healthcare resources and access to more efficient therapy.

In 2006 in Mexico, Del Angel-García *et al.* [17] performed the first comparison of the cost–effectiveness of carbetocin and oxytocin for prevention of bleeding after cesarean delivery. Their results showed that the mean cost per woman was significantly lower with carbetocin than with oxytocin. The study was only published as a summary and data are missing from the analysis.

Given the paucity of data on the cost–effectiveness of carbetocin, further research is necessary to address this important question, which is the subject of the present analysis.

The term quality-adjusted life year (QALY) was first used by Zeckhauser and Shepard in 1976 as a measure of health outcomes that combined duration and quality of life. A QALY is a unit of measure of an individual's preferences with respect to his/her quality of life after a healthcare intervention combined with the years of life gained with respect to a specific state of health. Therefore, QALYs are highly valued as a basic component in the evaluation of costs of healthcare interventions when taking decisions. QALYs have made it possible to resolve the lack of comparability of results when evaluating the usefulness of different healthcare programs in different healthcare areas [18]. The incremental cost–effectiveness ratio (ICER) considers the increased cost of gaining a QALY after the introduction of a new therapy or healthcare technology compared with the previous one. Therefore, it provides the cost per extra unit of the results of one healthcare strategy compared with another. The incremental cost–effectiveness threshold depends on the country where the study is performed. This information is not available for Peru. The WHO recognizes that a healthcare intervention is cost-effective if the cost per QALY is less than 3× gross domestic product (GDP) per capita. Since the GDP for the year 2015 in Peru was US$12,638 (World Bank), a cost-effective intervention would be to consider the gain of a QALY by comparing two alternatives of less than US$37,914, (S/. 132,699). The threshold defined for Colombia and Chile is 1× GDP per capita, although it must be remembered that the GDP per capita in these countries is greater than in Peru.

The objective of the present study was to compare the cost–effectiveness of carbetocin with that of oxytocin for the prevention of PPH after cesarean delivery by evaluating the results obtained from the literature and those obtained at Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru during the year 2015.

Materials & methods

We compared the alternatives evaluated in the Cochrane meta-analysis *"Carbetocin for preventing postpartum haemorrhage"* [16].

The clinical results were obtained from the studies in the meta-analysis that compared the use of carbetocin with oxytocin for the prevention of uterine hemorrhage after cesarean delivery (The Cochrane Library, 2012) and from the other bibliographic references of the present report [19,20].

We used this information to construct a decision tree, which was applied for the model (Figure 1).

The direct costs were obtained from the Office for Accounting and Costs of Hospital Nacional Edgardo Rebagliati Martins, mainly from the SAP R/3 system and correspond to the year 2015 (cost template in Excel).

Table 1 shows the costs that were taken into consideration for data processing.

It is noteworthy that drug costs were taken from the Peruvian official price list (DIGEMID-MINSA). The minimum price of the different products for the public sector was taken into consideration, with the exception of oxytocin, for which the average public sector price was calculated (in contrast with information for other drugs, the web page of the official price list gives a minimum and maximum price for oxytocin). The average price was S/. 0.825. The price of carbetocin was provided by the distributor of this product in Peru (S/. 62.5). All prices

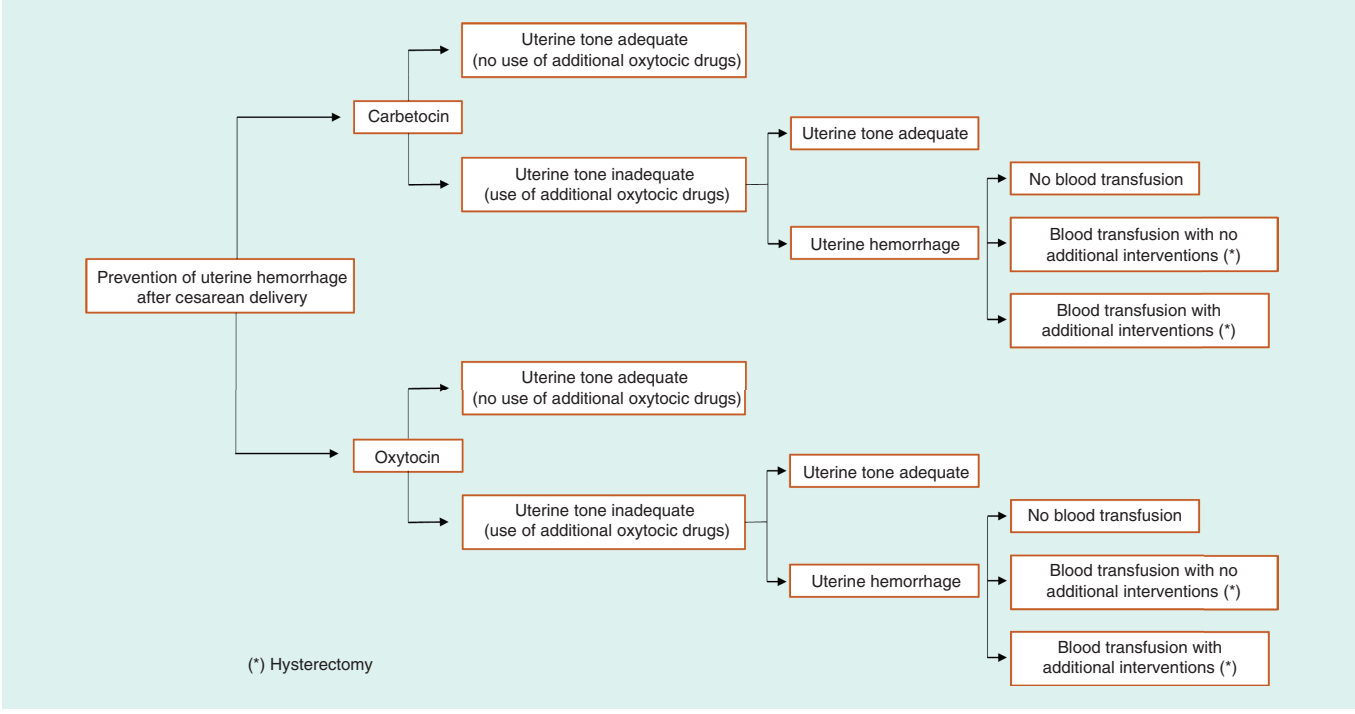

Figure 1. Decision tree.

Table 1. Costs of data processing.

Item	Unit cost in soles	Unit cost in soles (S/.)
Blood transfusion	312.57	643.13
Cost of hemorrhage kit	223.08	223.08
Cost of additional oxytocic drugs	16.67	16.67
Oxytocin	0.85	0.85
Misoprostol	2.25	2.25
Ergometrine	0.40	0.4
Duratocin (carbetocin)	62.07	62.07
Atropine	0.25	0.25
Hysterectomy	2845.01	2845.01

Costs are for every 100 patients.

include sales tax. The dose of oxytocin was that used in the study by Cordovani *et al.* [10] for prevention of uterine hemorrhage (6.5 ampoules).

An interview was held with the head of the Blood Bank to determine the costs of consumables for blood transfusions. Similarly, the cost of consumables for control of uterine hemorrhage was also calculated (posthemorrhage kit from Guía de Práctica Clínica de Manejo de la hemorragia de la segunda mitad del embarazo y postparto – ESSALUD 2014 [*Clinical Practice Guidelines on the management of hemorrhage during the second half of pregnancy and postpartum - ESSALUD 2014*]). An average of two transfusions were considered necessary to control uterine hemorrhage.

The costs included in the model were those of medication, hysterectomy and control of bleeding. The analysis was made from the payer's perspective.

The time horizon was 1 year (2015) for the calculation of QALYs. In Peru, there is no cost–effectiveness threshold for healthcare interventions.

The results of the model are provided based on a deterministic approach using the ICER. A series of sensitivity analyses were subsequently performed to determine the effect of uncertainty with respect to the parameters and to the

Table 2. Deterministic results.

Variables	Carbetocin	Oxytocin
Hemorrhages	3.398	13.729
Transfusions	0.072	0.363
Cost of hemorrhage (S/.)	758.06	3062.64
Cost of transfusion (S/.)	93.91	808.25
Total costs (S/.)	64,369.54	13,306.13
Total QALYs	833.88	832.86A

Number of hemorrhages for every 1000 patients.

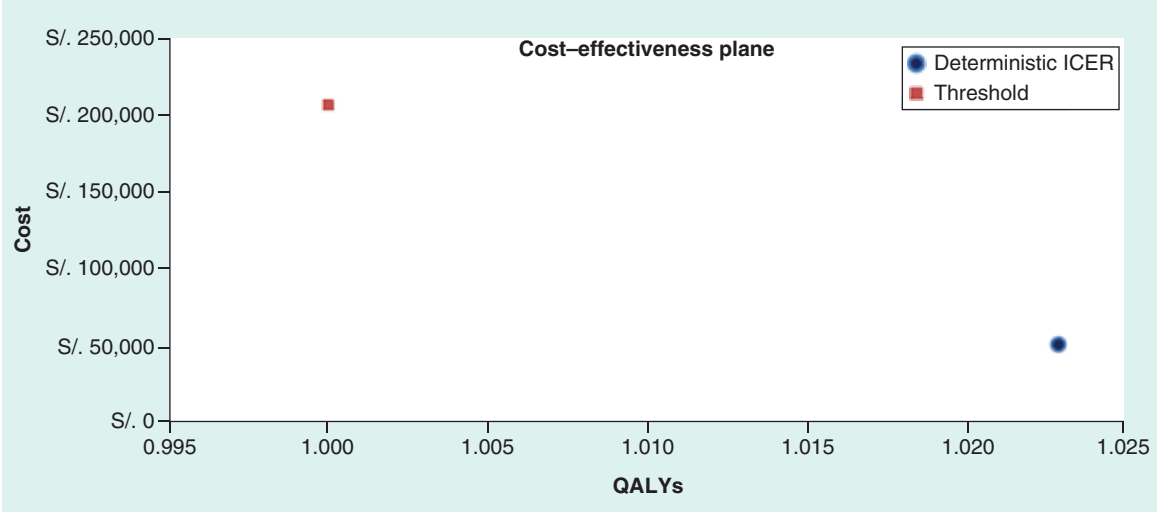

Figure 2. Cost–effectiveness.
ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life years.

structure. First, we performed a univariate sensitivity analysis in which the costs used in the model were increased and decreased by 10% to determine how the outcome changed (ICER). Second, we performed a probabilistic sensitivity analysis in which each parameter was assigned a probability distribution; a value for the distribution was taken randomly. This process was repeated 1000-times, and the mean value of the ICER was taken. Thus, it was possible to compare whether the uncertainty (variability) of the parameters used in the model generated changes in the result.

Excel 2013 was used to enter and process data according to the decision tree model.

Results

According to the meta-analysis examined in the present study, patients who received carbetocin require uterotonic agents significantly less frequently than patients who received oxytocin (relative risk: 0.64; 95% CI: 0.51–0.81) [16].

Carbetocin was clearly associated with fewer hemorrhages, fewer transfusions and, therefore, with lower costs stemming from these interventions (Table 2). Similarly, carbetocin was associated with a higher number of QALYs.

The resulting ICER was S/. 49,918 per QALY, that is, below the threshold we estimated for Peru, as observed on the cost–effectiveness plane (Figure 2).

The univariate analysis revealed the cost of carbetocin to be a relevant parameter in the model, leading the result to vary by only 10% for the base case. When the price of carbetocin varies (± 10%), the ICER increases or decreases by 12% without changing the direction of the result, that is, it does not change in favor of oxytocin. The remaining parameters do not vary the result (ICER) more than 1% (Figure 3).

This analysis was followed by a second analysis to investigate the change in the result depending on the relationship between the cost of oxytocin and the cost of carbetocin (cost of carbetocin/cost of oxytocin). The costs of both drugs were taken from studies performed in Colombia and the UK in order to analyze the ratio and its association

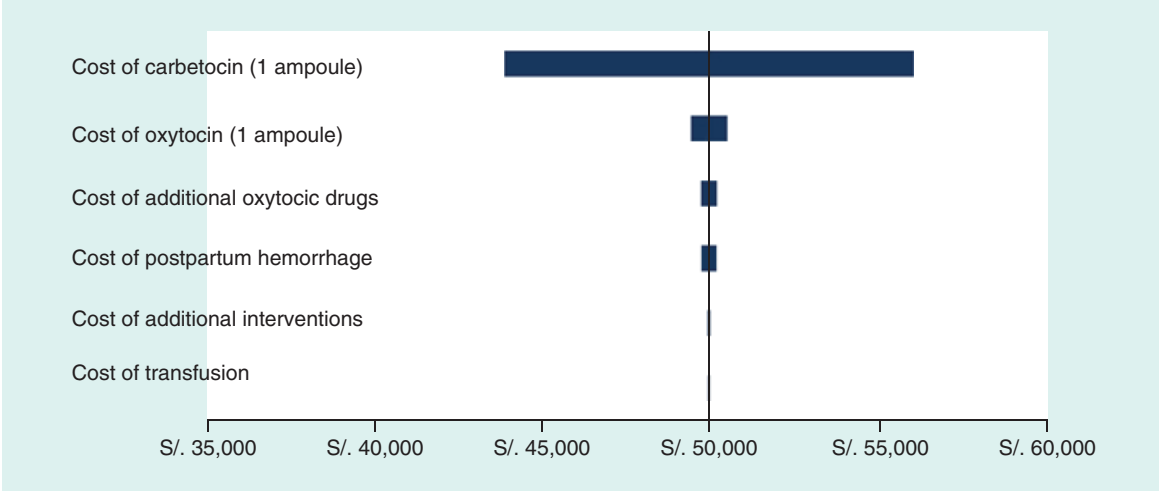

Figure 3. Univariate analysis: tornado diagram.

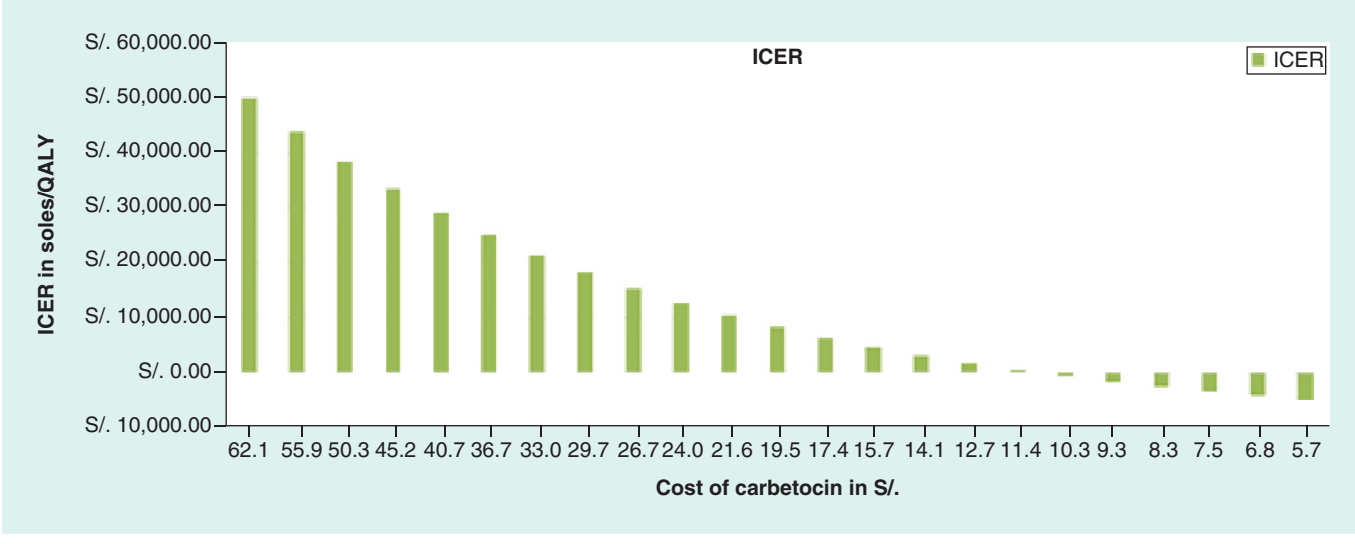

Figure 4. Association between the carbetocin/oxytocin ratio and the incremental cost–effectiveness ratio.
ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life years.

with the ICER. The results of the analysis can be seen in Figure 2, which shows that when the cost of carbetocin falls with respect to that of oxytocin, the ICER decreases. This means that in situations where oxytocin is more expensive, the price of carbetocin can be higher and lead to an ICER that favors carbetocin; however, in situations where oxytocin is inexpensive (e.g., in Peru), the price of carbetocin cannot be expensive, since the ICER increases considerably (Figure 4).

Discussion

Our results show that, when compared with oxytocin, therapy with carbetocin for the prevention of hemorrhage following cesarean delivery is associated with an ICER of S/. 49,918 per QALY, thus situating therapy with carbetocin below the cost–effectiveness threshold for the present study. It is important to remember that the greater cost of carbetocin in relation to oxytocin affects the result of the ICER.

Probabilistic sensitivity analysis indicates that carbetocin continues to be associated with fewer events (hemorrhages and transfusions) and, therefore, lower costs. It is also associated with the results of the deterministic analysis in terms of total cost. However, owing to the uncertainty surrounding the useful data, the ICER of the probabilistic

sensitivity analysis is S/. 119,178 per QALY, among others, carbetocin is more efficient than oxytocin: 51.7% of the iterations had an acceptance threshold of S/. 207,800 per QALY.

Similar studies performed in Canada [21], Colombia [22] and Mexico [17] show that therapy with carbetocin is a cost-effective option for the prevention of hemorrhage after cesarean delivery.

Conclusion

Carbetocin is safe and effective in clinical practice. In addition, it is more cost-effective than oxytocin for the prevention of uterine hemorrhage in women undergoing cesarean delivery, thus making it possible to avoid blood transfusion, additional uterotonic agents to control bleeding and, potentially, hysterectomy in extreme cases. Carbetocin also makes it possible to reduce the cost of these interventions.

Summary points

- Postpartum hemorrhage is one of the main causes of maternal death throughout the world.
- The risk of postpartum hemorrhage is much greater in cesarean delivery, especially in developing countries, where most operations are performed as emergency procedures.
- Prophylaxis with uterotonic agents significantly reduces the risk of postpartum hemorrhage.
- Carbetocin is more cost-effective than oxytocin for the prevention of postpartum hemorrhage in women undergoing cesarean delivery.
- Compared with oxytocin, administration of carbetocin makes it possible to avoid blood transfusion, additional uterotonic agents to control bleeding and hysterectomy.
- Probabilistic sensitivity analysis indicates that carbetocin is associated with fewer events (hemorrhages and transfusions) and, therefore, lower costs.
- Carbetocin is safe and effective in clinical practice.

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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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