World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Carbetocin (PABAL) and postpartum hemorrhage (PPH)

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World Journal of Advanced Research and Reviews, 2023, 19(03), 428–438

Publication history: Received on 30 July 2023; revised on 07 September 2023; accepted on 09 September 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.19.3.1811

Abstract

Objective: with the marketing in our country of the Carbetocin molecule for the prevention of postpartum hemorrhage which currently relies on the administration of Oxytocin, we tried to make a comparison of the effectiveness between the 2 products.

Method: review of the literature and studies made by comparing the 2 products.

Results: Carbetocin has been proposed in the prevention of uterine atony during Cesarean: Carbetocin (Pabal) is a synthetic analog of human oxytocin: its longer duration of action (approximately 5 hours instead of 1 hour 30 minutes for Syntocinon), and single dose make it a molecule of choice in the therapeutic strategy prevention of uterine atony.

Reliable and well-tolerated Carbetocin appears to be as effective as Oxytocin in clinical practice in preventing PPH.

Keywords: Carbetocin; Oxytocin; Uterine atony; Cesarean; Preventing PPH; Postpartum hemorrhage

1. Introduction

Postpartum hemorrhage remains a major cause of maternal morbidity and mortality, hence the importance of the speed and efficiency of the responders by following a clear pre-established strategy, it is essentially based at the beginning on medical treatment before proceeding, in case of failure, to surgical treatment, hence the interest of look for the risk factors and try to prevent this threatening emergency.

This prevention is currently based on the use of Oxytocin and with the marketing in our country of a new molecule which is Carbetocin (PABAL) which is a known treatment in France and other countries, we have sought a little bit in the literature and we consulted studies to make a comparison between the two products mentioned above and try to see the interest of one or the other.

At the beginning we make a small reminder on the haemorrhage of the delivery then we present some studies which gave an interest to study the Carbetocin by making the comparison with Oxytocin.

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2. Material and methods

2.1. Reminder

2.1.1. Definition

- Postpartum hemorrhage (PPH): blood loss greater than or equal to 500 ml after childbirth
- Severe PPH: blood loss greater than or equal to 1000 ml.

Major complication of childbirth.

- Exposes the woman to the complications of:
- Transfusion, resuscitation, infertility in case of hysteretomy (1/2000) and increases the risk post-traumatic stress

The clinical intervention threshold depends on:

- Bleeding rate
- And the clinical context because not all hemorrhages are externalized

Thus, it may be justified to start active CEP before the threshold of 500 ml of blood loss is reached:

- if the bleeding rate is high or the clinical tolerance poor.

Conversely, in the context of cesarean delivery, the action threshold can be fixed at a level of blood loss higher than that of 500 ml if clinical tolerance allows it.

2.1.2. HPP Epidemiology

- The incidence of PPH: 5% of deliveries when blood loss measurement is imprecise, and around 10% when blood loss is quantified.
- The incidence of severe PPH: around 2%.

2.1.3. Causes of postpartum hemorrhages

Uterine atony

- Leading cause of PPH, responsible for 50 to 80% of cases[1] , mechanical hemostasis does not occur or occurs poorly and results in profuse and potentially fatal bleeding.

Placental retention

- Second cause of PPH, involved in approximately 10 to 30% of PPH. [1]

Wounds of the genital tract

- Genital tract wounds are responsible for 15-20% of PPH;

Peri-genital hematoma or vaginal thrombus:

- 1 per 1,000 deliveries

Uterine ruptures: one case per 1,500 deliveries.

Uterine inversion

- A serious complication of delivery.
- It is rare, one in 100,000 deliveries.

Abnormalities of the placenta:

- Placenta previa: common cause (11%)
- Placenta accreta: 1/2,000 to 1/5,000 acc

Pathology of hemostasis.

Note that in the literature we find several risk factors for PPH. (Table 1)

Table 1 Main risk factors for PPH in the most recent population studies (modified from Deneux-Tharaux et al). [3]

Maternal characteristics pre-existing pregnancy	
Maternal age	
15–19 years	0.8 (0.6–1.1)
20–34	1
35–39	1.1 (1.0–1.2)
≥ 40 years	1.4 (1.1–1.7)
Primiparous	1.7 (1.4–2.0)
Grand multiparity	1.2 (0.8–1.9)
History of caesarean section	1.9 (1.4–2.6)
Features of pregnancy	
Multiple pregnancy	3.8 (2.2–6.5)
Polypolyhydramnios	1.9 (1.2–3.1)
IUI	2.5 (1.9–3.3)
Pregnancy hypertensive pathology	1.9 (1.2–2.8)
Features of labor and delivery	
Trigger	1.2 (1.0–1.5)
Prolonged labor	1.7 (1.4–2.0)
Episiotomy	2.2 (1.8–2.6)
Instrumental vaginal delivery	2.3 (1.5–3.4)
Caesarean section before labor	2.3 (2.1–2.6)
Caesarean section during labor	3.2 (2.4–4.2)
Macrosomia	1.7 (1.3–2.2)

2.1.4. Management of PPH

The management of a PPH is a race against time to save the lives of patients, it is a multidisciplinary management in a joint and simultaneous way: midwife, obstetrician, anesthetist, biologist and resuscitator, each in its place from the diagnosis and must be clear with the actions to be taken to optimize care without leaving room for improvisation.

She must follow the protocols established and adapted according to the context (and preferably displayed in the establishment), guided by the management algorithms established by the National College of French Gynecologists and Obstetricians (CNGOF) [1], published in 2014 and which distinguish between: management of PPH after vaginal delivery (figure 1), or during cesarean section (figure 2).

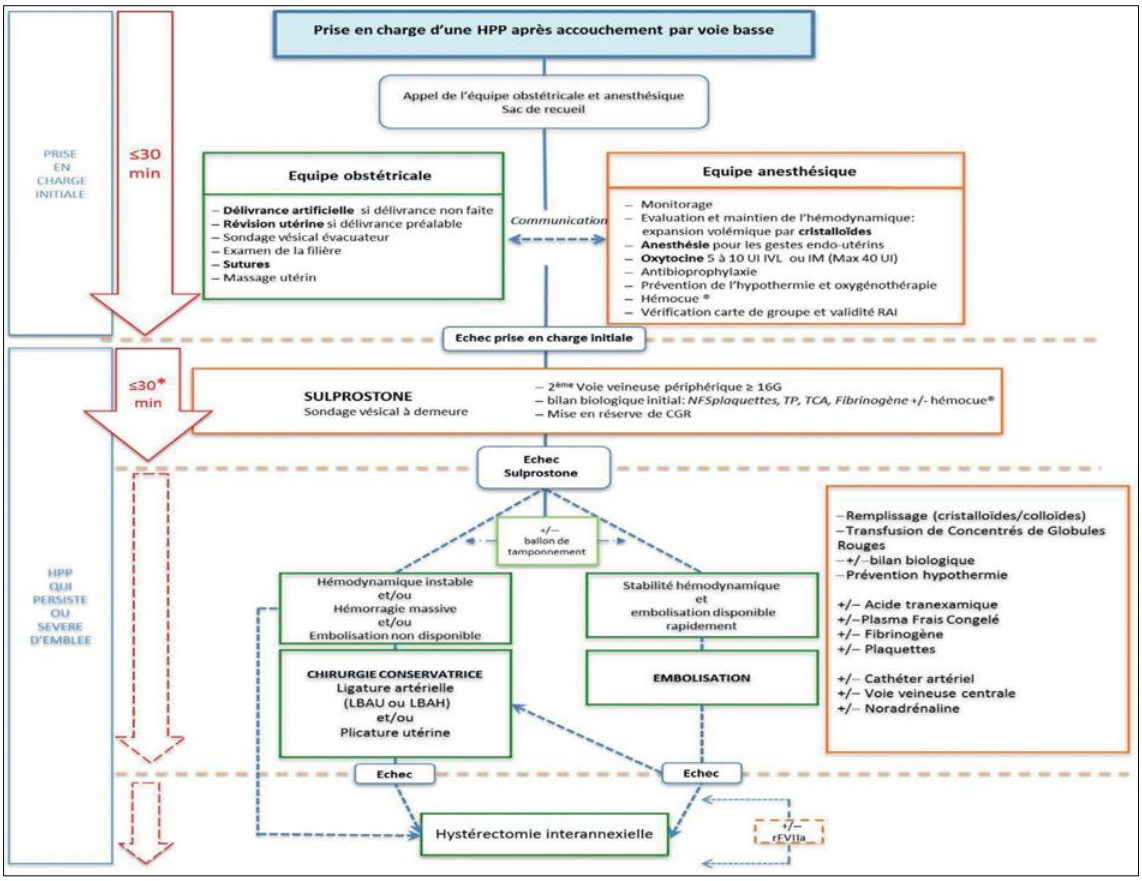

Figure 1 Management algorithm for postpartum hemorrhage after vaginal delivery developed by the CNGOF

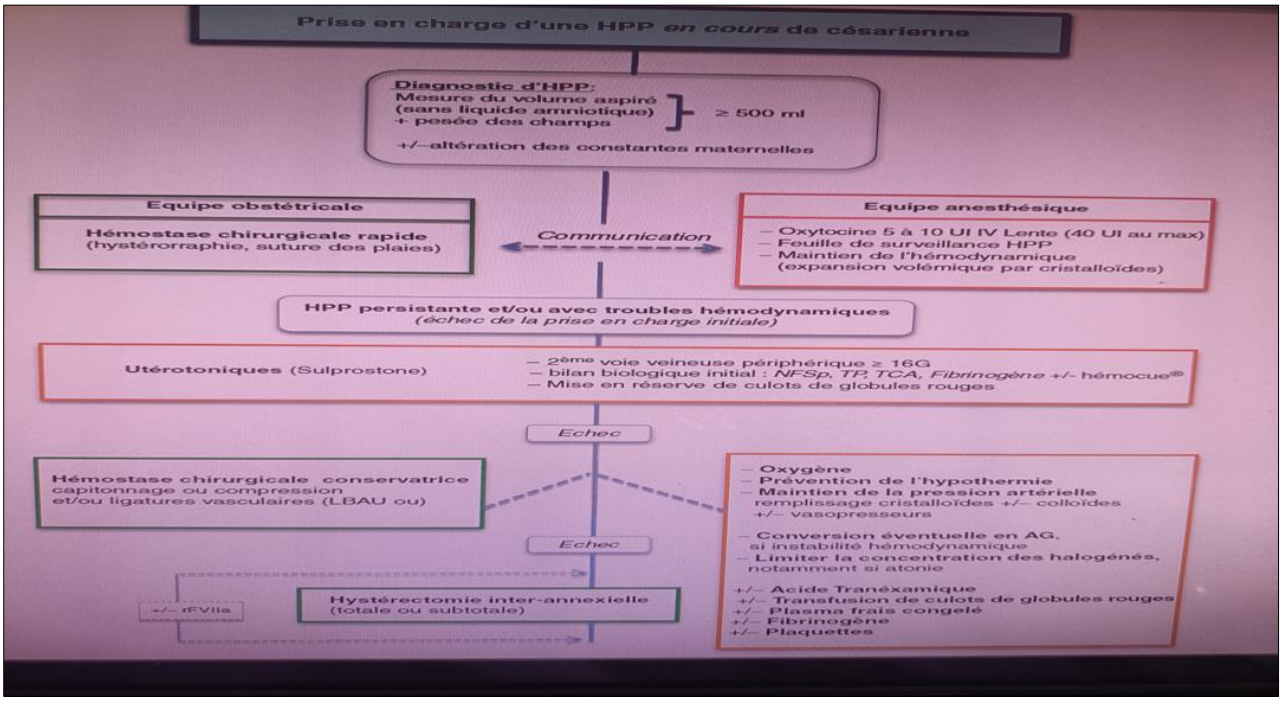

Figure 2 Management algorithm for postpartum hemorrhage during cesarean section developed by the CNGOF

2.1.5. PPH prevention [7]

Based on several axes:

a/ prevention of anemia:

- Aim to ensure that women approach childbirth without anemia.
- Moderate anemia (Hb < 10.5 g/dl): oral iron supplementation.
- Severe anemia (Hb < 8 g/dl) and/or poorly tolerated and/or imminent delivery: injectable iron supplementation (Ferinject) will be discussed.

b/ Patients with a coagulation pathology or with a rare blood type:

- Pregnancy follow-up in close collaboration with a doctor competent in hemostasis who will anticipate the specific care during childbirth
- Blood center

c/ Patients on anticoagulants/ antiplatelet agents

- In the event of anticoagulation at a preventive dose, the risk of PPH is not increased: a period of 12 hours since the last injection is recommended.
- Curative anticoagulation by LMWH is accompanied by an increased risk of haemorrhage and requires compliance with a time limit of more than 24 hours.
- Taking aspirin does not increase the frequency or intensity of PPH.
- d/ Directed delivery [5]
- normal delivery: systematically place a venous route from 5 cm of dilation; inject after release of the anterior shoulder 5 IU or 10 IU of slow direct IV oxytocin,
- cesarean delivery: a slow intravenous injection over at least one minute of 5 IU of oxytocin is recommended, systematic maintenance treatment with an intravenous infusion of oxytocin (10 IU in 500% of 5% serum glucose) can be undertaken without exceeding 10 IU per hour

2.2. Oxytocin versus carbetocin

Prevention of this atony currently relies on prophylactic injection of 5 to 10 IU of slow IV oxytocin during clamping of the umbilical cord during Caesarean section.

The initial intravenous injection is usually followed by a continuous infusion of oxytocin for several hours after caesarean section

Figure 3 Syntocinon

- Synthetic analog of human oxytocin.
- Longer duration of action (approx. 5 h vs. 1 h 30 for Syntocinon),
- It has a half-life of 40 minutes, giving it a longer duration of action than oxytocin.
- Its affinity for myometrial oxytocic receptors is identical to that of oxytocin.
- This molecule is used to prevent uterine atony following caesarean delivery.
- It is administered as a single dose (1 ml dose at 100 µg intravenously) after birth

Figure 4 Carbetocin: PABAL [6]

To compare the 2 products, we consulted the literature review and studies comparing the 2 products

3. Results and discussion

3.1. A study by F. Pizzagalli et al [8]

* Comparison between carbetocin and oxytocin during caesarean section in the prevention of post-partum hemorrhage

Whose main objective was to compare the efficacy of Carbetocin with oxytocin in directed delivery during caesarean section in 2 groups of 2 patients,(Oxytocin group)and(Carbetocin group),with almost the same characteristics (Table 2)

- 282 caesarean patients (Oxytocin group) underwent directed delivery by intravenous injection of 5 IU oxytocin (Syntocinon) at umbilical cord clamping, followed by an intraoperative infusion of 10 IU oxytocin. A further infusion of 10 IU oxytocin over 8 hours was maintained postoperatively.
- 262 caesarean patients (Carbetocin group) underwent directed delivery by a single slow intravenous injection of 100 mg carbetocin (Pabal) at the time of umbilical.

The primary endpoint was the hematocrit differential (results: table 3).

Secondary endpoints were hemoglobin differential, adjuvant use of sulprostone and surgical hemostasis (table 4).

Table 2 General population characteristics

	Oxytocin n = 282	**Carbetocin n = 262**
Primiparous	42.8% (n = 231)	43.5% (n = 114)
Multiparous	57.2% (n = 309)	56.5% (n = 148)
Gestational age 37 SA	90.6% (n = 489)	91.2% (n = 239)
Age > 35 years	21.3% (n = 115)	22.5% (n = 59)
Previous caesarean section	23.3% (n = 126)	25.9% (n = 68)
Multiple pregnancy	5% (n = 27)	4.2% (n = 11)
Placenta previa	3.5% (n = 19)	3.8% (n = 10)
Placenta accreta	0.7% (n = 4)	1.1% (n = 3)
Uterine malformation	0.6% (n = 3)	0.4% (n = 1)
Previous PPH	0.6% (n = 3)	0.4% (n = 1)
Duration of labor > 12 hours	1.7% (n = 9)	1.5% (n = 4)
Artificial induction of labor	24.6% (n = 133)	23.2% (n = 61)
Use of prostaglandins	5.2% (n = 28)	7.2% (n = 19)
Caesarean section before labour	33.7% (n = 182)	38.5% (n = 101)
Stagnation of dilation 2 hours	24.1% (n = 130)	28.6% (n = 75)

Chorioamniotitis	0.7% (n = 4)	1.9% (n = 5)
HRP	2.2% (n = 12)	2.3% (n = 6)
Uterine rupture	15% (n = 8)	1.5% (n = 4)
Fetal macrosomia	19.8% (n = 107)	19.8% (n = 52)

Table 3 Pre- and postoperative differences in hematocrit and hemoglobin levels

	Oxytocin (n = 540)	**Carbetocin (n = 262)**
Mean hematocrit differential	3.52 +/- 2.3	3.75 +/- 1.9
Hemoglobin differential between 2 and 4 g/dL	15.6% (n = 84)	6.5% (n = 17)
Hemoglobin differential 4 g/dL	0.4% (n = 3)	1.5% (n = 4)
PPH rates	21.6%	18.7 %

Table 4 Complementary treatments

	Oxytocin (n = 540)	**Carbetocin (n = 262)**
Sulprostone	5.9% (n = 32)	8.7% (n = 23)
Embolization/arterial ligation	0.7% (n = 4)	1.5% (n = 4)
Hemostasis hysterectomy	0.7% (n = 4)	1.5% (n = 4)
Red blood cell transfusion	3.5% (n = 19)	4.2% (n = 11)
Intravenous iron infusion (venofer1)	13.8% (n = 75)	6.8% (n = 18)

This study

- confirms the efficacy of carbetocin in clinical practice for the prevention of PPH following caesarean section.
- Showed a significant reduction in: hemoglobin losses between 2 and 4 g/dL and the need for intravenous martial supplementation.
- The clinical advantages of carbetocin, together with its single-injection mode of administration, make it a molecule of choice in the therapeutic strategy for the prevention of PPH.
- the only weakness in the current state of knowledge seems to be its high cost.

3.2. Another study by G. Triopon et al[9]

* Use of carbetocin for directed delivery during caesarean section. Comparison with oxytocin *

- To compare the efficacy of carbetocin with that of oxytocin, in the context of directed delivery during caesarean section.
- Data from 155 women who received carbetocin during caesarean section were compared with a cohort of 155 women who received oxytocin (Tables 5, 6 and 7).

The primary endpoint was the use of surgical hemostasis techniques (vascular ligatures, uterine cushioning, and hysterectomy) during Caesarean section. (Table 8)

Table 5 Characteristics of patients included in the study

	Carbetocin (n = 155)	**Oxytocin (n = 155)**
Parity	1.9	2.1
Gestité	2,3	2,6
Age in years	30.6	30.7
SA term	38.2	37.9
Caesarean section history (in %)	24.7	34.2
Previous PPH (in %)	0.6	0.5
Pre-caesarean Hb (in g/dl)	11.5	11.4

Table 6 Data concerning medications received by patients prior to Caesarean section, when performed during labor and/or in emergency

	Carbetocin (n = 154)	**Oxytocin (n = 155)**
Oxytocin induction	41.5 %	34.8 %
Cervical ripening with intra-vaginal prostaglandins	12.3 %	12.3 %
Use of tocolytics in the hours preceding caesarean section	7.1 %	10.3 %

Table 7 Data on postpartum patients

	Carbetocin = 138-154	**Oxytocin = 152-155**
Intravenous iron therapy (Venofer1)	6.5%	14.5
Transfusions of packed red blood cells	0.7%	1.3
Postoperative hemoglobin level belowthan 6 g/dL (%)	0.6	0.37
Postoperative hemoglobin level between 6.1 and 8 g/dL (in %)	5.8	9.7
Postoperative hemoglobin level between 8.1 and 9 g/dL (in %)	15.6	14.
Postoperative hemoglobin level above 9.1 g/dL (%)	78.6	74.8

Table 8 Additional treatments during Caesarean section after administration of uterotonic agent

	Carbetocin(%, n/153)	**Oxytocin(%,n/155)**
Uterine lining surgery	0.6	4.5
Ligation of internal iliac arteries	0.6	0.5
Ligation of uterine vessels	0.6	0.6
Uterine vessel ligation uterine vessels	0.6	0.5

The only difference observed in terms of surgery was in favour of carbetocin, with less recourse to uterine padding alone.

- The use of surgical uterine hemostasis techniques, which can be considered a relevant factor reflecting the extent of uterine atony and bleeding,

- The use of uterine padding techniques, which are the first measure to be implemented in the event of persistent uterine atony despite medical treatment, was less frequent in the Carbetocin group during this study,

In conclusion: Carbetocin appears to be as effective as oxytocin, and the use of uterine padding techniques was lower in the carbetocin group, but this difference was not significant.

3.3. Based on Thierry Harvey's paper [10] on: * new developments in the prevention of uterine atony * ,

emphasized that the reasons for using carbetocin instead of oxytocin (Syntocinon®) in the French Maternité des Diaconesses experiment, which has been going on for over a year, are essentially due to the product's pharmacodynamic and, above all, pharmacokinetic characteristics(Table 9)

Table 9 Pharmacology table

	Oxytocin	**Carbetocin**
Rhythmic uterine activity		
Duration of uterine contraction	8'	60'
Time Contractions:	16'	67'
T½	10 min	40 min
Immediate effects: (IV)	1 to 2 minutes Hypotension	< 2 minutes Bioavailability = 80%
Modes of administration	IM IV (bolus)	IV (infusion)

And concluded that

- The experience of the Diaconesses maternity hospital also shows that the routine use of carbetocin during caesarean sections is much simpler, since it only requires a single IV injection,
- Reliable, well tolerated (no vasomotor disturbances, some headache and nausea) and no transfusion required.
- Post-operative monitoring by nursing staff is also simplified,
- The same control of uterine globe tonicity was achieved with carbetocin and oxytocin, but carbetocin enabled faster withdrawal of the infusion and eliminated the need to control the infusion rate.
- The management of post-operative pain is identical with the 2 products.
- Carbetocin, with a single IV dose of 100 µg after Caesarean section extraction, maintains uterine tone and prevents excessive bleeding, without increasing adverse effects, and facilitates patient monitoring.

According to Jean Marie Manus of the journal Francophone des Laboratoires[11] , given that oxytocin must be stored at temperatures of 2 to 8 maximum, OMS proposes a replacement product with the same advantages in countries that do not have cold chain infrastructures, and according to a clinical trial, published in the Grand Journal of Medicine, by OMS with MSD FOR Mothers and Labo Ferring in 10 countries involving 30000 women: each woman randomly received a single injection of Carbetocin or Oxytocin in the immediate post-partum period, revealed that the 2 products were equally effective in preventing PPH, and the carbetocin formulation allows it to be stored at room temperature with efficacy of at least 3 years at 30 degrees and 75% humidity.

The development of a drug to prevent PPH that remains effective in hot, humid conditions is very good news for the millions of women giving birth in parts of the world without access to reliable refrigeration: Dr Meting of WHO's Reproductive Health and Research Department

3.3.1. other studies

- The use of carbetocin is currently validated in 23 countries.
- Nevertheless, 2 Canadian articles: have largely contributed to the democratization of its use, making it today a molecule of choice in the therapeutic strategy for the prevention of uterine atony, the cause of 58% of PPH: .
  - A/ Boucher et al. double-blind comparison of the effects of Carbetocin and oxytocin

Intraoperative blood loss.

And uterine tone in post-Caesarean patients.

The authors report that a single IV injection of 100 µg of carbetocin is as effective and more reliable than a 16-hour continuous infusion of oxytocin in preventing excessive blood loss after delivery of the placenta, but is also more likely to maintain adequate uterine volume and tone (golden globe of safety) for 24 hours.

Observed less uterine massage (during vaginal delivery) in the carbetocin versus oxytocin group.

- B/ Concerning carbetocin, Dansereau et al.

double-blind comparison of the same 2 products in the prevention of uterine atony after CS, in terms of the effects of a 100 µg dose of carbetocin and a standard continuous infusion, observed less frequent recourse to the use of uterotonic agents in the Carbetocin versus oxytocin group.

- All these observations would probably merit an overall cost study, in order to know the real additional cost of using this molecule routinely, since we know at present that it is less widely used than oxytocin, mainly because of its cost, which is almost ten times higher than that of oxytocin;
- Eliminating the need to prepare oxytocin infusions could simplify their preparation.
- which, in medical-economic terms, could be an argument for carrying out this overall cost study comparing the use of carbetocin versus oxytocin.

4. Conclusion

- Carbetocin has recently been proposed for the prevention of uterine atony during Caesarean section.
- Carbetocin (Pabal) is a synthetic analogue of human oxytocin: its longer duration of action (around 5 h instead of 1 h 30 for Syntocinon), and single dose make it a molecule of choice in the therapeutic strategy for the prevention of uterine atony.
- Carbetocin is reliable and well tolerated, and appears to be as effective as Oxytocin in clinical practice for the prevention of PPH.
- Carbetocin is not approved for use after vaginal delivery in France

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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