Title:

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Journal:

The Journal of Maternal-Fetal & Neonatal Medicine 2016

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

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To cite this article: Ahmed Mohamed Maged, AbdelGany MA Hassan & Nesreen AA Shehata (2016) Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women, The Journal of Maternal-Fetal & Neonatal Medicine, 29:4, 532-536, DOI: 10.3109/14767058.2015.1011121

To link to this article: https://doi.org/10.3109/14767058.2015.1011121

Published online: 03 Mar 2015.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, 2016; 29(4): 532–536
 DOI: 10.3109/14767058.2015.1011121

informa healthcare

ORIGINAL ARTICLE

Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women

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Abstract

Objective: To compare effectiveness and tolerability of carbetocin versus oxytocin in prevention of postpartum hemorrhage (PPH) after vaginal delivery.
Methods: A prospective double-blinded randomized study conducted on 200 pregnant women randomized into two groups: Group 1 (100 women) received single 100 μg IM dose of carbetocin and Group 2 received of 5 IU oxytocin IM. Both groups received their drug after fetal and before placental delivery.
Results: There was a statistically significant difference between the two study groups regarding amount of bleeding (337.73 ± 118.77 versus 378 ± 143.2), occurrence of PPH (4 versus 16%), need for other uterotonics (23 versus 37%) and hemoglobin difference between before and after delivery (0.55 ± 0.35 versus 0.96 ± 0.62) (all being lower in carbetocin group) and measured hemoglobin 24 h after delivery (being higher in carbetocin group); however, there was no significant difference between the two study groups regarding occurrence of major PPH and the need for blood transfusion. Women in carbetocin group showed a statistically significant lower systolic and diastolic blood pressure immediately after delivery and at 30 and 60 min than women in oxytocin group. There was no significant difference between the two study groups regarding occurrence of nausea, vomiting, flushing, dizziness, headache, shivering, metallic taste, dyspnea, palpitation and itching. Women in carbetocin group experienced tachycardia more than women in oxytocin group.
Conclusions: Carbitocin is a better alternative to traditional oxytocin in prevention of PPH after vaginal delivery with minimal hemodynamic changes and similar side effects.

Keywords

Carbetocin, oxytocin, postpartum hemorrhage, vaginal delivery

History

Received 1 January 2015
Accepted 20 January 2015
Published online 3 March 2015

Introduction

Postpartum hemorrhage (PPH) is best defined and diagnosed clinically as excessive bleeding that makes the patient symptomatic and/or results in signs of hypovolemia [1]. The most common definition of PPH is estimated blood loss $\geq$ 500 ml after vaginal birth. The inadequacy of this definition was illustrated in studies that assessed blood loss using various objective methods: the mean blood loss reported after vaginal delivery was approximately 400 to 600 ml, and clinicians were likely to underestimate the volume of blood loss [2].

The incidence of PPH has been reported to be 3.9% in women who delivered vaginally [3].

Risk factors for PPH include prolonged labor (>12 h), severe anemia, preeclampsia, antepartum hemorrhage, intrapartum blood loss, history of PPH or retained placenta, body mass index (BMI) >35, polyhydramnios, multiple gestation and difficult instrumental delivery [4,5]

Systematic reviews have concluded that active management of the third stage of labor, particularly the prophylactic use of uterotonic agents can significantly decrease the incidence of PPH compared with that of expectant management [6–8].

Oxytocin is the most widely used uterotonic agent [9–11], but has a half-life of only 4–10 min [12], that is why it is better administered as a continuous intravenous infusion to achieve sustained uterotonic activity [7,13].

Carbetocin is a synthetic long-lasting oxytocin agonistic analogue with prolonged half-life prolonging its pharmacological effects [14]. Its prolonged uterine activity may theoretically offer advantages over oxytocin in the management of the third stage of labor. The side-effect profile of carbetocin was not found to be different from that of oxytocin [15], but may prove to be advantageous when compared to Syntometrine [10].

The aim of this study was to compare the effectiveness and tolerability of carbetocin versus oxytocin in the prevention of

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PPH after vaginal delivery in women with at least two risk factors of atonic PPH.

Material and methods

This study was a prospective double-blinded randomized, with balanced randomization (1:1) and parallel grouped study, it was conducted on 200 pregnant women attending Kasr Al Ainy and Benisuef maternity hospitals during the period from May 2013 to December 2014. A control group was not included for ethical reasons.

The study was approved by local ethics committee and informed consents about the study and expected value and outcome were obtained. All participants were at 37–40 weeks of gestation with at least two risk factors for developing atonic PPH. Women were approached in the antenatal clinic or early in labor if appropriate. Risk factors included previous PPH, Primipara >40 years, BMI >35, multiple pregnancy, prolonged labor >12 h, and ultrasound estimated fetal weight >4 kg. Participants with placenta previa, coagulopathy, preeclampsia, cardiac, renal, liver diseases, epilepsy, and known hypersensitivity to oxytocin or carbetocin were excluded.

All patients were subjected to full history taking, general, abdominal and obstetric examination. Ultrasound scan, complete blood picture, liver functions and coagulation profile were also done.

Participants were equally randomized using automated web-based randomization system ensuring allocation concealment into two groups: Group 1 included 100 women who received a single 100 μg IM dose of carbetocin (Pabal® Ferring, West Drayton, UK) and group 2 included 100 women who received 5 IU IM oxytocin (Syntocinon®, Novartis, Basel, Switzerland). Both drugs were administered after delivery of the posterior shoulder, in cases of twin pregnancy the drugs were given after delivery of the second twin.

All participants were followed-up for 24 h. The uterine tone and amount of bleeding were noted and the need for further uterotonic agents was checked 2 min after giving the drug. Blood loss was estimated by weighing the swabs and using pictorial charts. PPH was defined as bleeding >500 ml and major PPH was defined as bleeding >100 ml. Blood hemoglobin was assessed 24 h after delivery.

Systolic and diastolic blood pressures were measured immediately after delivery, 30 and 60 min after delivery. We recorded possible complications like nausea, vomiting, tachycardia, flushing, dizziness, headache, shivering, metallic taste, dyspnea, palpitation and itching.

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using independent *t*-test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. *p* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL) release 15 for Microsoft Windows (2006).

Results

The 200 patients were classified into two groups: Group 1 included 100 patients who received carbetocin and group 2 included 100 patients who received oxytocin.

Baseline characteristics of the groups are summarized in Table 1. There was no significant difference between the groups in age, gravidity, parity, body mass index, gestational age and fetal birth weight.

Risk factors for atonic and traumatic PPH were not significantly different between the groups (Table 1).

There was no significant difference between the groups regarding the duration of 1st, 2nd and 3rd stages of labor (Table 1).

The amount of bleeding, occurrence of PPH, need for other uterotonics, the difference between blood hemoglobin levels before delivery and 24 h after delivery were significantly lower in the carbetocin group. On the other hand, there was no significant difference between the two groups regarding occurrence of major PPH and the need for blood transfusion (Table 2).

Women in the carbetocin group had a statistically significant lower systolic and diastolic blood pressure immediately after delivery, at 30 and 60 min after delivery (Table 3).

Regarding drugs side effects, there was no significant difference between the two groups regarding occurrence of nausea, vomiting, flushing, dizziness, headache, shivering, metallic taste, dyspnea, palpitations and itching. The incidence of tachycardia was significantly higher in the carbetocin group (Table 4).

Discussion

Our results have shown that carbetocin is superior to oxytocin in prevention of PPH after vaginal delivery in women with at least two risk factors for developing atonic PPH. This fact can be explained by the known longer half-life of Carbetocin when compared to Oxytocin causing a more uterine response, in terms of frequency and amplitude of uterine contractions [14].

Table 1. Baseline characteristics of the groups*.

	Carbetocin	Oxytocin	*p* value
Age (years)	32.84 ± 7.52	33.87 ± 7.6	0.337
Gravidity	1.59 ± 1.15	1.54 ± 1.07	0.752
Parity	1.54 ± 1.14	1.45 ± 1.04	0.502
BMI (kg/m^2)	28.78 ± 5.58	27.22 ± 5.81	0.054
Gestational age (weeks)	39.4 ± 1.35	39.2 ± 1.4	0.333
Risk factors for atonic PPH*			
History of PPH	54	60	0.391
Fetal macrosomia (>4000 gm)	45	50	0.479
Prolonged labor (>12 h)	62	57	0.471
Twin pregnancy	13	14	0.836
APH	1	2	1
Risk factors for traumatic PPH*			
Episiotomy	26	22	0.508
Lacerations	2	3	0.651
Duration of 1st stage (h)	13.39 ± 3.38	12.98 ± 3.31	0.388
Duration of 2nd stage (min)	91.8 ± 20.85	87.8 ± 19.67	0.165
Duration of 3rd stage (min)	4.75 ± 2.05	4.56 ± 2.1	0.519
Fetal birth weight (g)	3.63 ± 0.64	3.61 ± 0.65	0.0.854

*Data are presented as mean ± SD.
BMI, body mass index; PPH, postpartum hemorrhage.

Two substantive studies comparing active management of third stage with expectant management have clearly indicated the advantages of active management. The Bristol trial [16], in which active management had been the norm, and the Hinchingbrooke trial [17], in which expectant management had been the norm, both studies demonstrated significant reductions in the incidence of PPH with active management compared with expectant management (5.9% versus 17.9% and 6.8% versus 16.5%, respectively). Both studies were terminated after interim analysis because the difference in PPH rate was so great.

Reyes et al. performed a prospective double-blinded randomized controlled trial in 60 women with severe preeclampsia who were randomized to receive either oxytocin or carbetocin during the third stage of labor. They found that carbetocin was as effective as oxytocin in the prevention of PPH. Carbetocin had a safety profile similar to that of oxytocin, and it was not associated with the development of oliguria or hypertension. They concluded that carbetocin is an appropriate alternative to oxytocin for the prevention of PPH in women with severe preeclampsia [18].

That difference between our results and those of Reyes et al. may be attributed to the difference in the studied population. Reyes et al were studying women with severe preeclampsia but we have excluded women with preeclampsia from our study.

In our study, we found that the amount of bleeding after delivery was significantly lower in women who received carbetocin than those who received oxytocin (Figure 1). We also found less need for additional uterotonics and less difference between hemoglobin before and after delivery among women in the carbetocin group.

Boucher et al. have randomized 160 women undergoing vaginal delivery with at least one risk factor for PPH to receive either carbetocin 100 µg IM or oxytocin 10 IU iv oxytocin infusion over 2 h. The need for uterine massage and other uterotonics were significantly lower in the carbetocin group, these results agreed with ours. However, they found no significant difference in the amount of bleeding or the hemoglobin difference before and after delivery between the groups. The difference between these results and our scan can be explained by the difference in the route and dose of oxytocin used in our study and that of Boucher et al. [19].

Attilakos et al. have randomized 377 women undergoing cesarean sections to receive either IV carbetocin 100 µg or IV oxytocin 5 IU after the delivery of the baby. The carbetocin group needed significantly less uterotonic results, which agrees with our findings. On the other hand, they found no significant difference in the blood loss or difference in hemoglobin before and after the operation between the two groups. This disagrees with our results and the reason may be

Table 4. Drug complications*.

	Carbetocin ($n = 100$)	Oxytocin ($n = 100$)	p value
Nausea	3	1	0.621
Vomiting	2	0	0.497
Tachycardia (h >100 b/min)	10	2	0.017
Flushing	1	0	1
Dizziness	2	0	0.497
Headache	5	2	0.445
Shivering	2	0	0.497
Anemia	29	27	0.753
Metallic taste	1	0	1
Dyspnea	1	0	1
Palpitations	2	1	1
Itching	1	0	1

*Data are presented as number and percent.

Table 2. Bleeding and Hb results of the groups*.

	Carbetocin	Oxytocin	p value
Amount of bleeding (ml)	337.73 ± 118.77	378 ± 143.2	0.03
PPH (>500 ml)†	4%	16%	0.037
Major PPH (>1000 ml) †	0%	1%	0.316
Need for other uterotonics†	23%	37%	0.031
Need for blood transfusion†	1	2	1
Hb before delivery (g/dl)	11.01 ± 1.3	11.11 ± 1.24	0.581
Hb 24 h after delivery(g/dl)	10.51 ± 1.38	10.13 ± 1.26	0.04
Hb difference (before and after delivery) (g/dl)	0.55 ± 0.35	0.96 ± 0.62	<0.001

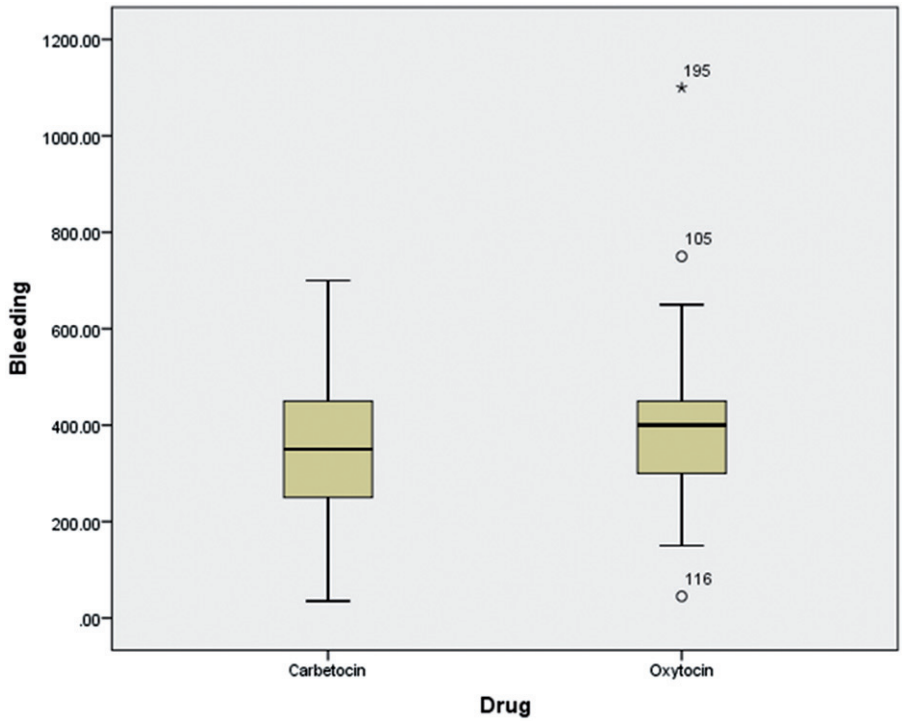
*Data are presented as mean ± standard deviation.
†Data are presented as number and percent.

Table 3. Blood pressure measurements in the groups*.

		Carbetocin	oxytocin	p value
Systolic blood pressure (mmHg)	Immediately after delivery	110.25 ± 6.39	117.51 ± 9.71	<0.001
	30 min after delivery	108.06 ± 6.64	115.19 ± 10.28	<0.001
	60 min after delivery	112.57 ± 6.67	118.42 ± 9.49	<0.001
Diastolic blood pressure (mmHg)	immediately after delivery	73.38 ± 3.7	76.67 ± 4.73	<0.001
	30 min after delivery	74.22 ± 3.78	80.7 ± 10.89	<0.001
	60 min after delivery	74.87 ± 3.8	76.96 ± 4.89	0.001

*Data are presented as mean ± SD.

Figure 1. Amount of bleeding in the groups.



in the difference in the studied populations, we studied women with risk factors for atonic PPH undergoing vaginal delivery, but Attilakos et al studied women undergoing cesarean sections with or without risk factors for PPH [15].

Leung et al. compared the efficacy and safety of intramuscular (IM) carbetocin with IM syntometrine in preventing primary PPH in a prospective, double-blinded, randomized controlled trial. They found that IM carbetocin was as effective as IM syntometrine in preventing primary PPH after vaginal delivery. It was less likely to induce hypertension and had a low incidence of adverse effect. So, it should be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labor [20].

In our study, there was a significantly lower blood pressure (affecting both systolic and diastolic blood pressure) immediately after delivery and at 30 and 60 min after delivery among women in carbetocin group than women in oxytocin group. These results agree with those of Samimi et al. who randomized 200 women undergoing vaginal delivery to receive either carbetocin or syntometrine, they found that the systolic BP measurements at 0, 30, and 60 min after delivery were significantly higher in the syntometrine group [21].

Moertl et al. studied 56 women undergoing elective cesarean section after spinal anesthesia. They measured hemodynamic parameters taken for 500 s upon administration of a slow intravenous bolus of 100 μg of carbetocin or 5 IU of oxytocin to prevent PPH. They found a non-significant difference in the hemodynamic effects of both drugs, with a maximal effect at about 30–40 s: HR increased 17.98 ± 2.53 bpm for oxytocin and 14.20 ± 2.45 bpm for carbetocin. Systolic blood pressure (sBP) decreased (-26.80 ± 2.82 mmHg for oxytocin versus 22.98 ± 2.75 mmHg for carbetocin). Following the maximal effect, women treated with carbetocin recovered slowly to baseline values asymptotically (HR and BP), whereas women treated with oxytocin displayed a slight rebound bradycardia at 200 s (-6.8 ± 1.92 bpm). Patients under both treatments showed a similar profile of side effects without any indication of unexpected adverse effects. They concluded that both oxytocins have comparable hemodynamic effects and are uterotonic drugs with an acceptable safety profile for prophylactic use. Minimal differences in the recovery phase beyond 70 s are in keeping with the fact that carbetocin has an extended half-life compared with oxytocin [22].

The difference between our results and those of Moertl et al. can be attributed to the difference in sample size between the studies. We studied 200 women but Moertl et al. studied 56 women only. The difference can be also due to the use of spinal anesthesia in the study of Moertl et al. Another difference is in the studied population, Moertl et al. studied women undergoing elective cesarean section, but we have studied women undergoing vaginal delivery with at least two risk factors of atonic PPH.

We did not find a significant difference between the two study groups regarding drugs side effects apart from tachycardia being more common in women who received carbetocin than those who received oxytocin. These results agree with those of Moertl et al. [22] and Attilakos et al. [15], who found no significant difference in the side effects between carbetocin and oxytocin.

To the best of our knowledge, our study is the first study comparing carbetocin effectiveness, safety and hemodynamic effects with oxytocin after vaginal delivery in women with at least two risk factors of developing atonic PPH.

We concluded that carbetocin is a better alternative to traditional oxytocin in prevention of PPH after vaginal delivery in women with at least two risk factors for atonic PPH with minimal hemodynamic changes and similar side

effects and could be routinely used to prevent PPH, which represents the main deaths among parturient women.

Declaration of interest

The authors declare no conflicts of interests.

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