BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Injection of Intraumbilical Carbetocin versus Oxytocin in the Management of Retained Placenta

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Received: 20 February 2024

Accepted: 12 April 2024

Abstract

Background: Although oxytocin is the most widely accepted uterotonic agent in addition to other drugs, however, which agent is ideal for retained placenta has yet to be clearly identified. Carbetocin is a synthetic long-acting oxytocin analogue that has been recommended for management of retained placenta. **Aim of the work:** Compare the efficacy of intraumbilical carbetocin versus oxytocin in the management of retained placenta. **Patients and methods:** The current study included 92 pregnant women with failure to deliver the placenta after 30 minutes after delivery of the baby. They were randomly divided to receive either intraumbilical injection of carbetocin or oxytocin. The cases were followed up and the different outcomes regarding the efficacy of both drugs were reported. **Results:** The incidence of successful separation of placenta was statistically significantly higher in the carbetocin group. The Time of separation of placenta was statistically significantly shorter in the carbetocin group . The need manual removal of placenta was statistically significantly higher in the oxytocin group. The amount of blood loss was statistically significantly lower in the carbetocin group . The incidence of blood transfusion was statistically significantly higher in the oxytocin group. The need for additional drugs was statistically significantly higher in the oxytocin group. **Conclusion:** In cases with RP, carbetocin outperformed oxytocin in terms of placenta separation success, removal time, haemoglobin level drop, blood loss, transfusion need, and side effects.

Key words: Retained placenta; Oxytocin; Carbetocin.

Introduction

The third stage of labour starts when the foetus is delivered fully and ends when the placenta and its attached membranes are expelled in their entirety [(1)].

It usually lasts between five and fifteen minutes during the third stage of labour. The third stage of labour is considered prolonged if it lasts longer than 30 minutes after the foetus is delivered [(2)].

During this time, postpartum haemorrhage is the most common problem that can arise. One of the reasons of postpartum haemorrhage is placental retention caused

by uterine atony, which prolongs the third stage of labour [(3)].

The third stage of labour also brings the possibility of retained placenta (RP). A high risk of haemorrhage is associated with this condition, which occurs in 0.2 to 1% of deliveries [(4)].

Current treatment for placental retention is manual delivery, which is safer in an operating room with anaesthesia. If these conditions are not met, mortality can reach 10%. Hormonal cascades and uterine contractions separate these layers and expel the placenta during birth [(4)].

WHO recommends prophylactic administration of 10 IU oxytocin 2 min after foetus delivery, immediate umbilical cord clamping, and controlled traction to prevent postpartum haemorrhage for the third stage of labour [(5)].

Umbilical vein oxytocin injection for RP was found ineffective by a Cochrane review ***(6)***. A UK, Uganda, and Pakistani double-blind, placebo-controlled trial found that umbilical vein oxytocin injection did not reduce placenta removal [(7)].

Carbetocin, a synthetic oxytocin analogue, has a longer half-life, reducing the need for infusions after the initial dose. Carbetocin is more stable than oxytocin and can avoid early decomposition by disulfidase, aminopeptidase, and oxidoreductases due to its structure. When administered postpartum, carbetocin prolongs uterine contraction amplitude and frequency compared to oxytocin [(8)].

Patients and methods

This is a prospective randomized interventional study that was conducted at Obstetrics and Gynecology Department, Benha University Hospital during the period from October 2021 to September 2022. The study was approved by the Ethics Committee of Faculty of Medicine, NICU of Benha university hospitals and Benha Insurance hospital, Benha, Egypt {M.S.11.11.2021}.

The study included 92 Pregnant women with retained placenta who were randomly divided into two groups, as follows, Carbetocin Group that included 46 pregnant females who received intraumbilical injection of carbetocin after failure to deliver the placenta after 30 minutes after delivery of the baby and Oxytocin Group that included 46 pregnant females who received intraumbilical injection of oxytocin after failure to deliver the placenta after 30 minutes after delivery of the baby.

The study included pregnant female at or beyond 37 weeks of gestation with singleton pregnancy and cephalic presentation, achieved vaginal delivery, preterm labour and second trimester abortion failed to deliver the placenta after 30 mins of cord clamping.

The cases with the following criteria were excluded; previous CS, placenta accreta, trapped placenta, previous myomectomy, maternal hemodynamic instability (pulse ≥ 120 beat/min, or a decrease in diastolic blood pressure of more than 20mm hg after delivery), postpartum hemorrhage, antepartum hemorrhage, prolonged labor (>20h), accelerated labor (<3h), patients liable to postpartum hemorrhage, chorioamnionitis, instrumental delivery (forceps and vacuum), medical disorders (cardiac disease, anemia, hypertension and diabetes) and pregnant women who

receive anticoagulant therapy, or those with thrombocytopenia.

.The study follows 2013 Helsinki Standards [9]. The local research committee, Faculty of Medicine, Benha University, approved the study, and the included cases gave written informed consent.

Full medical history, obstetric history and detailed physical examination were checked. Patients with placenta adherence (placenta not delivered for 30 minutes after cord clamping) received intraumbilical injection of either Oxytocin 20 IU in 30 ml saline (0.9%) or 1ml Carbetocin (containing 100 mcgm carbetocin) in 30 ml saline, the medications were injected directly in the umbilical vein after clamping. The injection was performed with a 50-mL syringe and an 18-gauge needle approximately 1–2 cm from the introitus, the solution was injected slowly over 1 minute, and at the end of the injection, the solution was milked toward the cord insertion.

At 30 and 45 min after administration of the medication, or in the case of clinical signs of placental separation, an attempt to deliver the placenta was made. If the final attempt to deliver the placenta (45 minutes after administration of the study medication) failed, manual removal was performed in the operating theatre.

The duration needed to deliver the placenta is the main outcome measured by stopwatch starts once we inject the drug, then the amount of blood loss which was measured by evaluation of the drop in hemoglobin and hematocrit level by comparing the hemoglobin concentration and hematocrit value on admission and before discharge, using this equation:

$$\text{Blood loss} = \text{BV} \times \frac{(\text{Hct}_\text{i} - \text{Hct}_\text{t})}{\text{Hct}_\text{i}}$$

Hct_i = initial Hct

Hct_t= target Hct

Blood volume = weight (kg) × 75 ml ***(10).***

Vital signs readings immediately after the medication and repeated at 30 and 60 min were recorded.

Outcome Measures:

The outcomes included successful separation of placenta, time of separation of placenta, need manual removal of placenta, change in the hemoglobin level, amount of blood loss, need for blood transfusion, and need of additional drugs and side effects of the drug use.

Statistical analysis

SPSS 26 for Windows® program was used to code, process, and analyze the data. Qualitative data were presented as number and percent. The Chi-Square (or Monte-Carlo) test compared groups with categorical data. The quantitative data were presented as mean ± SD and range. To compare two groups with normally distributed quantitative variables, independent samples t-test was used and Mann Whitney Test (U test) if the data were abnormally distributed. Paired samples t-test was used to compare two dependent groups of quantitative variables at wo different time points. P values <0.05 are considered significant.

Results

The current study included 92 pregnant women with failure to deliver the placenta after 30 minutes after delivery of the baby. They were randomly divided into two

groups; group C (Carbetocin Group) who received intraumbilical injection of carbetocin and group O (Oxytocin Group) who received intraumbilical injection of oxytocin. There was no statistically significant difference between the studied groups in age, weight, height or BMI (Table 1)

Table (2) shows that 28.3% of C group was PG while in O group 39.2% were G. Most frequent parity in both groups was 1 to 3 (75.8% in C group & 92.8% in O group). Frequency of previous abortion was 42.4% in C group & 42.9% in O group. Mean GA was 31.48 & 29.48 weeks in Group C & O respectively. There were no statistical significance differences between the studied groups in gravidity, parity, previous abortion or gestational age.

There was a statistical significance (p=0.03) increase frequency of success in C group compared to O group (69.6% versus 47.8%). There was a statistical significance decrease (P=0.001*) in time of separation of placenta in C group compared to O group (16.99 versus 21.84 min). There was a statistical significance (p=0.03) increase in frequency of manual removal of placenta in O group compared to C group (52.2% versus 30.4%). There was a statistical significance increase in frequency of using other drugs among O group compared to C group (21.7% versus 6.5%). There was a statistical significant decrease (p=0.004) in blood loss among C group compared to O group (629.79 versus 779.42 ml). There was a statistical significant increase in frequency of blood transfusion among O group compared to C group (17.4% versus 4.3%) (Table 3).

There were no statistical significance differences between the studied groups in Hb level immediately before delivery . But there was a statistical significance increase in Hb level in Carbetocin Group compared to Oxytocin Group (P=0.04). Regarding differences between before delivery & post-partum in each group there was a highly statistical significance decrease in Hb level post-partum compare to before delivery in both groups but % of reduction is higher in O group compared to C group (14.46% versus 11.43%) (Table 4).

Table (1): Demographic data of the studied groups:

Variable		Carbetocin Group (*n*=46)	Oxytocin Group (n=46)	P
Age: (years)	*Mean ± Sd*	28.22±5.98	26.91±5.62	0.28
	Range	20-29	18-40	NS
Weight: (kg)	*Mean ± Sd*	75.48±13.55	73.76±11.14	0.51
	Range	54-109	59-105	NS
Height: (cm)	*Mean ± Sd*	163.04±4.24	162.57±5.49	0.61
	Range	155-171	155-175	NS
BMI: (Kg/m^2)	*Mean ± Sd*	28.49±5.53	27.66±4.56	0.44
	Range	21.36-43.66	20.18-37.5	NS

Table (2): Obstetric History of the studied groups:

Variable		Carbetocin Group (*n*=46)		Oxytocin Group (n=46)		
		No	**%**	**No**	**%**	**P**
Gravidity	*PG*	13	28.3	18	39.2	
	2-4	29	63	26	56.5	0.54
	5-7	3	6.5	2	4.3	NS
	>7	1	2.2	0	0	
Parity:		(n=33)		(n=28)		
	0	5	15.2	1	3.6	
	1-3	25	75.8	26	92.8	0.30
	4-6	2	6	1	3.6	NS
	>6	1	3	0	0	
Previous abortion:		(n=33)		(n=28)		
	No	19	57.6	16	57.1	0.97
	Yes	14	42.4	12	42.9	NS
GA: (weeks)	*Mean ± Sd*	31.48±7.31		29.48±6.97		
	Range	23-41		18-41		0.18 NS

Table (3): Management outcome among the studied groups:

Variable		Carbetocin Group (*n*=46)		Oxytocin Group (n=46)		
		No	**%**	**No**	**%**	**P**
Outcome:	Succeed	32	69.6	22	47.8	**0.03***
	Failed	14	30.4	24	52.2	
Time of separation of placenta: (min)	*Mean ± Sd*	16.99±5.02		21.84±5.50		
	Range	10.9-33		10.35-34.05		**0.001***
Need manual removal of placenta	*No*	32	69.6	22	47.8	**0.03***
	Yes	14	30.4	24	52.2	
Other drug use:	No	43	93.5	36	78.3	**0.03***
	Yes	3	6.5	10	21.7	
Blood loss: (ml)	*Mean ± Sd*	629.79±176.16		779.42±299.59		**0.004***
	Range	299.67-966.67		314.17-1689.51		
Blood transfusion:	*No*	44	95.7	38	82.6	**0.04***
	Yes	2	4.3	8	17.4	

Table (4): Hemoglobin level among the studied cases immediately before delivery & immediately post-partum management:

Variable		Carbetocin Group (*n*=46)	Oxytocin Group (n=46)	P
Hb immediately before delivery: (gm/dl)	*Mean ± Sd*	10.81±0.59	10.84±0.67	0.80
	Range	9.7-11.6	9.7-11.7	NS
Hb immediately post partum: (gm/dl)	*Mean ± Sd*	9.52±0.61	9.26±0.58	**0.04***
	Range	8.5-10.8	8.5-10.3	
Paired t		**20.14**	**19.35**	
P		**<0.001****	**<0.001****	
% of reduction		**11.43%**	**14.46%**	

This table shows that frequency of complications among C group was 2.2% while in O group was 4.3% without statistical significance difference between the two groups(Table 5).

Table (5): Sid effects of used drugs among the studied groups:

Side effects	Carbetocin Group (*n*=46)		Oxytocin Group (n=46)		
	No	%	No	%	P
No	45	97.8	44	95.7	
Nausea & vomiting	0	0	2	4.3	0.22
Headache & hot flashes	1	2.2	0	0	NS

Discussion:

The current study was conducted to compare the efficacy of intraumbilical carbetocin versus oxytocin in the management of retained placenta.

The current study included 92 pregnant women with failure to deliver the placenta after 30 minutes after delivery of the baby. They were randomly divided into two groups; group C (Carbetocin Group) who received intraumbilical injection of carbetocin and group O (Oxytocin Group) who received intraumbilical injection of oxytocin.

In the current study we chose to use 1ml Carbetocin (containing 100 µg carbetocin) in 30 ml saline. In the studies to date, the choice of dose has largely been empirical. Previous studies have primarily used a dose of 10–20 IU oxytocin, although doses of up to 100 IU have also been reported *(11)*.

In the current study, there was no statistically significant difference between the two groups regarding the anthropometric measurement and the obstetric history. This indicates the process of good randomization to avoid the selection bias.

In the current study, there was a statistical significance (p=0.03) increase frequency of success in C group compared to O group (69.6% versus 47.8%). Also, there was a statistical significance decrease (P=0.001) in time of separation in C group compared to O group (16.99 versus 21.84 min).

This agreed with who included a total of 200 women who were divided into two groups; each 100 women. The first group received intra-umbilical vein injection of 1 mL carbetocin (containing 100 µg carbetocin) diluted in 20 mL normal saline 0.9% and the second group received intra-umbilical vein injection of 20 IU oxytocin diluted in 20 mL normal saline 0.9%. The results showed that the duration of the third stage of labor (minutes) were significantly lower in carbetocin group when compared to oxytocin group *(12)*.

This was also in accordance with who managed RP either by intraumbilical oxytocin, intravenous carbetocin, or sublingual misoprostol. The overall success rate was 66.7% (64/96), 71.3% (67/94), and 63.7% (58/91) for oxytocin, carbetocin, and misoprostol groups, respectively (P > 0.05). When time needed to achieve placental delivery considered, a significant difference was observed with the shortest time for carbetocin (16.61±3.76 min), then oxytocin (18.28±3.34 min), and lastly misoprostol (23.00±3.38 min) (P <0.001) *(13)*.

Within the same line, used I.V. bolus of 100-µg carbetocin and 50 IU oxytocin during the management of RP. They showed that the success rate of the carbetocin group was 86.84% compared to

77.5% in the intra-umbilical oxytocin group (p<0.05) [14].

Also, included a total of 132 women randomly allocated to receive either 20 IU oxytocin infusion (n = 66) or 100 μg carbetocin shot (n = 66) after fetal expulsion. They showed that the time of the third stage of labor was 33.4±20.4 minutes in the oxytocin group & 23.1±16.8 minutes in the carbetocin group (p=0.002) [15].

A previous report revealed that once the oxytocin crosses the syncytiotrophoblast, it enters the retroplacental lakes that drain into the radial veins and then into the uterine vein. Thus, the oxytocin might not enter the capillaries where it would be absorbed into the myometrium until its second passage around the body. Moreover, oxytocin could be deactivated by the oxytocinase, which is present in large quantities in the placental bed [16].

In the current study, there was a statistical significance (p=0.03) increase in frequency of manual remove in O group compared to C group (52.2% versus 30.4%).

This came in accordance with who showed that the incidence of manual removal of placenta was 9% in the carbetocin group and 17% in the oxytocin group, with statistically significant difference between the two groups [12].

In agreement with the current study, showed that eight patients (12.1%) in oxytocin group had complete placental retention versus two patients (3.0%) in carbetocin group ($p = 0.05$). Eight patients (13.8%) received oxytocin had remnants of placenta compared to four patients (6.2%) received carbetocin ($p = 0.04$). Sixteen patients (24.2%) received oxytocin and six patients (9%) received carbetocin needed surgical curettage ($p = 0.04$) ***(15)***.

However, in a study by There were no significant differences between the two groups regarding the need for manual removal of the placenta.[14].

In the current study, there was a statistical significance increase in the postoperative Hb level in Carbetocin Group compared to Oxytocin Group (P=0.04). Regarding differences between pre & post in each group there was a highly statistical significance decrease in Hb level post compared to pre in both groups but % of reduction is higher in O group compared to C group (14.46% versus 11.43%).

This came in accordance with who showed that the postoperative Hb concentration (g/dl) was significantly higher in carbetocin group (P value 0.03). Also there was a highly significant difference (P value 0.0001) between both groups as regard change in Hb concentration (g/ dl) 6 h after delivery with less change in the carbetocin group [12.

However, the current results disagreed with who showed that there were no significant differences between the two groups regarding the drop of hemoglobin within the first 48 h [14]. The variations should be explained due to difference in the sample size.

In this study, there was a statistical significant decrease (p=0.004) in blood loss among C group compared to O group (629.79 versus 779.42 ml). Also, there was a statistical significant increase in frequency of blood transfusion among O group compared to C group (17.4% versus 4.3%).

This copes with who showed that the total blood loss (ml) was significantly lower in carbetocin group (P value 0.04) when compared to oxytocin group. They also reported that the occurrence of postpartum hemorrhage (P value 0.045) and the need for blood transfusion (P value 0.03) was significantly lower in the carbetocin group. [12].

Within the same context, showed that Regarding the amount of blood lost during the third stage, patients in the oxytocin group lost a mean of 206.9 ± 35.2 ml of blood while the patients in the carbetocin group lost a mean of 87.2 ± 33.7 ml of blood (p = 0.001) [15].

However, according to the results of the author did not demonstrate any differences between the two groups in the amount of estimated blood loss after inclusion, the incidence of primary PPH or the need for additional uterotonic injection. The average drop in hemoglobin within 48 h was 1.32 ± 1.02 g/dL in the carbetocin group and 1.57 ± 1 08 g/dL in the intra-umbilical oxytocin group, and this difference was not significant; this drop indicates a positive effect of both uterotonic agents in reducing peripartum bleeding complications [14].

In the current study, there was a statistical significance increase in frequency of using other drugs among O group compared to C group (21.7% versus 6.5%). This can be explained by that the locally used carbetocin has more powerful and sustained uterotonic effects when compared with the locally administered oxytocin.

This was in accordance with who showed that the need for additional uterotonic drugs following complete placental delivery (in the carbetocin group, only 18 cases needed additional uterotonics and 82 did not need any additional uterotonics. However, in the oxytocin group, 69 cases needed additional uterotonics and 31 did not need any additional uterotonics) was significantly lower in the carbetocin group (P value 0.033) [12.

In 2019, conducted a RCT that included 100 subjects involved in the analysis. They aimed to make a comparison between oxytocin and carbetocin regarding the uterotonic effect. They found that oxytocin was inferior to carbetocin in the decrease of the need for additional contraction of the uterus either for vaginal delivery or for cesarean delivery as we found in our analysis [17]. Similar results were obtained by who showed that carbetocin group needed less additional uterotonics to achieve adequate uterine contractions (P <0.001) [18].

In the current study, frequency of complication among C group was 2.2% while in O group was 4.3% without statistical significance difference between the two groups.

In the study conducted by most of the patients did not suffer any side effects; 41 patients (62%) of the oxytocin group and 45 patients (68%) of the carbetocin group. Side effects experienced by patients were as follows comparing oxytocin to carbetocin group: nausea (seven patients versus four patients), vomiting (two patients versus three patients), headache (eight patients versus nine patients), backache (two patients in each group) and abdominal pain (six patients versus three patients) with no significant statistical difference (p = 0.72). All participants were followed-up until discharge from the

hospital, with no single recorded case of intra-uterine infections [15].

These results were similar to who compared IV 100 mg carbetocin with IV 10 IU oxytocin in cesarean sections, and concluded that carbetocin is well tolerated with great hemodynamic stability [19].

In another prospective case–control study, compared women received an IV bolus of 100 mg carbetocin with women in the control group who received 20 IU of oxytocin IV infusion in cesarean section. Both drugs had a hypotensive effect. Specifically, systolic and diastolic blood pressures were lower in the oxytocin group [20].

Also, in their systematic review on the use of uterotonics noted that intravenous carbetocin was associated with nausea (21–27%), abdominal pain (40%), itching (10%), flushing (26%), vomiting (7–9%), and feeling of warmth (20%), headache (3–14%), tremors (11%), and hypotension. In the current study, none of the patients experienced hypotensive effect in both groups. However, other reported side effects for carbetocin and oxytocin were nausea and vomiting (10% versus 13%), headache (13% versus 12%), backache and lower abdominal pain (7% versus 12%), respectively [21].

Overall, the current study revealed the efficacy of carbetocin over oxytocin in management of retained placenta in terms of higher success, less use of additional drugs, short duration for the process of separation and good hemodynamic profile.

The half-life of oxytocin is shorter than carbetocin which may explain the superiority of carbetocin. Having heat-safe storage in low-resource environments and heat stability for transport is another advantage of carbetocin [22].

Conclusion:

A major risk of excessive blood loss during childbirth is retained placenta, a potentially fatal complication. Carbetocin was better than oxytocin in cases with RP regarding more successful separation of placenta, lower time of separation of placenta, less need manual removal of placenta, less drop of the hemoglobin level, lower amount of blood loss, less need for blood transfusion and lower side effects.

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To cite this article: Mai H. Zahra, Mohammed A. Farag, Ali A. Morsy, Ali A. Bendary. Injection of Intraumbilical Carbetocin versus Oxytocin in the Management of Retained Placenta. BMFJ 2024;41(4):162-171.