Comparative Study between Carbetocin versus Oxytocin and Ergometrinein Prevention of Post-Partum Haemorrhage

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Abstract: Objective: The study aims at evaluation of effect of carbetocin in preventing postpartum haemorrhage compared with oxytocin and ergometrine. **Study Design:** Double-blind randomized single center study. **Setting:** This study was carried out at Sayed Galal University Hospital between March 2014 to June 2015. **Patients and Methods:** The study population consists of 100 pregnant patients attending emergency unit for delivery between completed 37 weeks and 41 weeks of gestation of non-complicated pregnancy. Undergoing elective or urgent caesarean section under regional anesthesia was randomly divided into two equal groups: **Group A:** included Fifty womens injected intravenously by one ml solution of 100µg carbetocin (Pabal®, Ferring) over one minute immediately after fetal delivery. **Group B:** included Fifty womens injected intravenously by 10IU oxytocin (syntocinon®, Novartis) plus 0.5mg ergometrine (Methergine®, Novartis) immediately after fetal delivery. **Results:** There is no significant difference between both groups regarding primary outcome (primary PPH), blood transfusions, fall in hematocrit ($P > 0.05$). Significantly, more women need additional uterotonic drugs in the oxytocin and ergometrine group than carbetocin group (42% versus 14%); P value < 0.05, Oxytocin (bolus or infusion) was the additional uterotonic drug for the majority of women. Uterotonics failed to prevent and control PPH in 7 patients (three patients in carbetocin group and four patients in oxytocin and ergometrine group) who required further surgical management, this difference was statistically non-significant ($P > 0.05$). **Conclusions:** Both drugs are equally effective in prevention of atonic postpartum hemorrhage. However, a single injection of carbetocin appears to be more effective than oxytocin and ergometrine to reduce use of additional oxytocic agents.

[Hassan Ahmed Abdrabo**. Comparative Study Between Carbetocin Versus Oxytocin And Ergometrinein Prevention Of Post-Partum Haemorrhage.** *Nat Sci* 2016;14(5):113-118]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 16. doi:10.7537/marsnsj14051616.

Keywords: carbetocin, oxytocin, postpartum hemorrhage

1. Introduction

Hemorrhage after delivery, or postpartum hemorrhage, is the loss of greater than 500 ml of blood following vaginal delivery, or 1000 ml of blood following cesarean section. It is the most common cause of perinatal maternal death in the developing world and is a major cause of maternal morbidity worldwide (1).

Primary postpartum haemorrhage (PPH) is the most common form of major obstetric haemorrhage. The traditional definition of primary PPH is the loss of 500 ml or more of blood from the genital tract within 24hours of the birth of a baby. PPH can be minor (500–1000 ml) or major (more than 1000 ml).Major could be divided to moderate (1000–2000 ml) or severe (more than 2000 ml) (2).

Postpartum hemorrhage prevention is very important. Several studies have shown that the use of uterotonic agents after placental separation can reduce the incidence of PPH by up to 30% - 40% and use of these drugs for PPH prevention is approved by all researchers (3).

The first uterotonic drug was ergometrine that introduced in 1950, while oxytocin and syntometrine were released during 1953 and 1963, respectively. Syntometrine is a combination of 5 IU oxytocin and 0.5 mg ergotamine in every 1 ml. This mixture is one of the most common uterotonic drugs that are used during the third stage of labour, because this drug has the rapid onset of action of oxytocin and the continuous effect of ergometrine (4).On the other hand, carbetocin was introduced during 1987 (5).

Carbetocin is a long-acting synthetic octapeptide analogue of oxytocin with agonist properties. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions and increased uterine tone. In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic uterine contractions within two minutes, lasting six minutes, followed by rhythmic contractions for a further hour. Intramuscular injection produced tetanic contractions in less than two minutes, lasting about 11 minutes, and followed by rhythmic contractions for an additional two hours (6).

2. Patients and Methods

A prospective double blinded randomized study was done after approval by the internal ethical committee of Al Azhar University. This study was carried out at Sayed Galal University Hospital. The study population consists of 100 pregnant patients attending emergency unit for delivery by caesarean section between completed 37 weeks and 41 weeks of gestation of non-complicated pregnancy.

Womens included in the study were divided into 2 groups:

First group:

Fifty womens injected intravenously by one ml solution of 100µg carbetocin (Pabal®, Ferring) over one minute immediately after fetal delivery.

Second group:

Fifty womens injected intravenously by 10IU oxytocin (syntocinon®, Novartis) plus 0.5mg ergometrine (Methergine®, Novartis) immediately after fetal delivery.

Inclusion criteria:

Single viable pregnancy, Non complicated pregnancy, Use of Spinal Anaesthesia and Full term pregnancy between completed 37weeks till 41weeks of gestation. The gestational age was determined based upon the date of the first day of last normal menstrual period and confirmed by ultrasound scan during the 1st trimester.

Exclusion criteria:

Cases of complicated pregnancy, Known or suspected sensitivity to oxytocin or ergometrine, Pregnancy Induced Hypertension, Impaired liver function, Coagulation disorders, Multiple pregnancies and uterine or cervical rupture.

All cases in the study subjected to Personal history, menstrual history, Obstetric history and Past history.

General examination, abdominal examination, Local examination and Assessment of the fetus were done.

Investigations:-

Upon admission Blood samples drawn to check for hemoglobin levels, random blood sugar, blood group and Rh for saving blood.

Blood loss was estimated postoperatively by giving each woman of each group standard 2 dressings (standard weight of dressing is 25 gm) during 24 hrs postoperative hospital stay and recording weight of blood soaked dressings and volume of lost blood.

The volume of lost blood was estimated by:

Weighing the soaked dressings which were prepared for the study as following:

* Weight of blood in a dressing in grams = weight of dressing after removal – weight before application (about 25gm).

* Volume of lost blood in ml = weight of blood in dressings in gm / 1.06 Where (1.06) is the density of whole blood. It's assumed that weight is due only to blood and not environmental water or debris (14).

The side effects of each drug as nausea, vomiting, shivering and headache or others were noted.

All the resulting data from the two groups collected tabulated and analyzed statistically.

The statistical analysis

Collected data were computerized and analyzed using Statistical Package for Social Science (SPSS) version 16 under windows 7.

3. Results

Womens included in the study (100 patients) were divided into 2 groups: First group:-

Fifty womens injected intravenously by one ml solution of 100µg carbetocin (Pabal®, Ferring) over one minute immediately after fetal delivery.Second group:-Fifty womens injected intravenously by 10IU oxytocin (syntocinon®, Novartis) plus 0.5mg ergometrine (Methergine®, Novartis) immediately after fetal delivery.

As shown in table **(1)** the mean age (years)for carbetocin group is 25.84±2.76 and for oxytocin and ergometrineis27.02±3.38, the mean BMI for carbetocin group 27.58±3.04while for oxytocin and ergometrine group is27.04±2.83, there were no significant statistical differences between both groups.

Table **(2)** show that seven cases (14%) in carbetocin group need additional uterotonic while twenty one cases (42%) in oxytocin and ergometrine group Therefore, significantly more women required additional uterotonics in the oxytocin and ergometrine group.

As shown in table **(3)**three patients in carbetocin group need further surgical intervention as modified B lynch suture and internal iliac artery ligation while for oxytocin and ergometrine group two patients need modified B lynch suture and two patients need uterine artery ligation and internal iliac artery ligation this difference was statistically non-significant.

As regards Hb difference between pre and 24hs postoperative, the mean Hb difference in carbetocin group was 0.712±0.24 and in oxytocin and ergometrine group was 1.14±0.31 this difference was statistically significant. Similarly there was significant difference in the estimated blood loss between the two groups (586±143 in carbetocin group versus 688±156 in oxytocin and ergometrine group) as shown in table **(4).**

As regards Complications four patients in carbetocin group had primary PPH three of them transfused with blood while in oxytocin and ergometrine five patients had primary PPH four of

them transfused with blood and Hysterectomy for intractable postpartum hemorrhage occurs in one patient as shown in table**(5).** These results was statistically non-significant.

Table (1): Demographic and characteristic data of participants.

Variable	Drug	Mean	SD	Min	Max	P value
Age (years)	Carbetocin	25.84	2.76	18	42	0.059 NS
	oxytocin and ergometrine	27.02	3.38	18	42	
BMI (kg/m^2)	Carbetocin	27.58	3.04	21	33	0.36 NS
	oxytocin and ergometrine	27.04	2.83	18	38	

Table (2): Comparison between two groups as regards need for additionaluterotoinic drugs.

Group / Variable	Carbetocin (n = 50)	Oxytocin &ergometrine. (n = 50)	P VALUE
20 I.U Oxytocin +2mg ergometrine. (No--%)	4 (8.0%)	11 (22.0%)	0.021 sig
Misoprostol 800mcg rectal. (No--%)	3 (6.0%)	10 (20.0%)	0.011 sig
Total (No--%)	7(14%)	21(42%)	sig

Table (3): Comparison between two groups as regards need for further surgical intervention.

Group / Variable	Carbetocin (n = 50)	Oxytocin &ergometrine. (n = 50)	P VALUE
Compression sutures. (modified B. lynch suture). (No--%)	2 (4%)	2 (4%)	0.5 NS
Uterine artery ligation (No--%)	1 (2%)	2 (4%)	0.27 NS
Internal iliac artery ligation. (No--%)	1 (2%)	2 (4%)	0.27 NS

Table (4): Comparison between two groups as regards Hb difference between pre and 24hs postoperative Hb level and estimated blood loss.

Group / Variable	Carbetocin (n = 50)	Oxytocin &ergometrine. (n = 50)	P VALUE
Preoperative Hb (mean±SD).	10.67±0.35	10.54±0.33	0.062 N sig
Postoperative Hb (mean±SD).	9.96±1.19	9.4±1.04	0.013 sig
Hb difference (mean).	0.712±0.24	1.14±0.31	0.001 sig
Estimated blood loss (ml). (mean±SD).	586±143	688±156	0.001 sig

Table (5): Comparison between two groups as regards Complications.

Variable / Group	Carbetocin (n = 50)	Oxytocin &ergometrine. (n = 50)	P value
Women transfused with blood: n (%) range	3 (6%) 500-1000	4 (8%) 500-1500	0.27 NS
Primary PPH n (%)	4 (8%)	5 (10%)	0.27 NS
Secondary PPH n (%)	0	0	-
Hysterectomy	0	1 (2 %)	-

4. Discussion

The aim of our study is to compare between patients undergoing caserean delivery taking carbetocin and those receiving oxytocin and ergometrine for prevention of PPH.

The study population consists of 100 pregnant patients attending emergency unit for delivery between completed 37 weeks and 41 weeks of gestation of non complicated pregnancy.

The current study demonstrated that there is no significant difference between both groups regarding maternal age, BMI, (P > 0.05). This agree with (zakaria M, et al; 2012) who perform A prospective double blinded randomized study on 200 patients at Beni-suef University.

The present study shows that 14 % of women in the carbetocin group needed additional uterotonics versus 42% of women in the Oxytocin & ergometrine group. Therefore, Significantly, more women need additional uterotonic drugs in the oxytocin & ergometrine group than carbetocin group (42% versus 14%); P value < 0.05, Oxytocininfusion plus egometrine (20I.U Oxytocin +2mg ergometrine) and rectal Misoprostol 800mcg was the additional uterotonic drugs for the majority of womens. These results agree with other previous studies; (Dansereau et al., 1999, Attilakos et al., 2010 and Larciprete et al., 2013)

Dansereau et al., (1999) performed RCT on 694 patients undergoing elective cesarean section, comparing the incidence of PPH in women who received either carbetocin as a 100 mcg IV bolus or oxytocin as a continuous infusion for 8 hours (25 IU of oxytocin in 1000 mL of Ringer's lactate, 125 mL per hour). The carbetocin group had a decreased incidence of PPH and of the need for therapeutic oxytocics (4.7% vs. 10.1%; P < 0.05).

Attilakos and colleagues (2010) in their double-blind RCT, womens received either carbetocin 100 mcg or oxytocin 5 IU intravenously after the delivery of the baby. Use of additional oxytocics was at the direction of the operating obstetrician. Significantly more women needed additional oxytocics in the oxytocin group (45.5% versus 33.5%, Relative risk 0.74, 95% CI 0.57-0.95). Carbetocin was associated with a reduced use of additional oxytocics. It is unclear whether this may reduce rates of PPH and blood transfusion.

Larciprete and colleagues' (2013) performed a study to compare the hemodynamic effects of oxytocin and carbetocin and to assess the efficacy of these two drugs in terms of blood loss and the additional uterotonic needed in caesarean section at high risk of primary postpartum hemorrhage. Women either received 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV (150 mL/hour) or carbetocin100 mcg IV bolus. More womens needed additional uterotonic agents in the oxytocin group (23.5% vs. 0%, p<0.01), though there was no significant difference in estimated blood loss and in the dropped hemoglobin level (p>0.05). There was a significant difference in the diuresis, higher in carbetocin group (1300 ml ± 450 ml vs. 1100 ml ± 250 ml, p=0.01). They reach to conclusion that a single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to prevent the PPH, with a similar hemodynamic profile and minor antidiuretic effect. But don't agree with what published by Boucher et al., 2004.

Boucher et al., (2004) performed a randomized, double-blind study which was conducted at 2 hospital centers, included 160 women with at least one risk factor for PPH. 83 women received 100 mcg carbetocin IM immediately after placental delivery, while 77 women received oxytocin IV infusion. Population profile and risk factors for PPH were similar for each group. No significant difference was observed in the number of women requiring additional uterotonic medications (12 in each group).

The lower use of additional uterotonic drugs is an important outcome with possible financial savings if the additional oxytocic requires prolonged administration on the labour ward or in the recovery area. However, this may be offset by the higher cost of carbetocin in comparison to oxytocin.

Our study shows that Uterotonics failed to prevent and control PPH in 7 patients (three patients in carbetocin group and four patients in oxytocin & ergometrine group) who required further surgical intervention. In carbetocin group: three patients had atonic postpartum hemorrhage which managed surgically by Compression sutures (B. lynch suture)in two of them and Internal iliac artery ligation in one of them.

In Oxytocin & ergometrine. Group: four patients had atonic postpartum hemorrhage which managed surgically by Compression sutures (B. lynch suture)in two patients and Internal iliac artery ligation in two patients.

When comparing pre- and 24 hours post-operative hemoglobin (HB) between both groups' results showed that there was no significant difference in the mean values of Preoperative Hb level (P > 0.05). While there was significant difference between both groups as regard postoperative hemoglobin level. this disagree with what published by (Dansereau et al., 1999) who concluded that The difference between the 2 groups in terms of hemoglobin drop and platelet count postoperatively was trivial and is of no clinical importance.

Regarding estimated blood loss between both groups results are statistically significant. This agree with what demonstrated in previous study by (Boucher M et al., 1998) performed A double-blind randomized study involving pregnant women undergoing cesarean section was conducted to compare the effectiveness of a single 100 micrograms intravenous injection of the long-acting oxytocin analog, carbetocin, with that of a standard infusion of oxytocin with respect to intraoperative blood loss, he concluded that A single 100 micrograms intravenous injection of carbetocin was as effective as a continuous 16 hour infusion of oxytocin in controlling intraoperative blood loss after placental delivery. Mean blood loss after carbetocin administration was 29 ml less than after oxytocin administration ($p = 0.3$).

This also agree with what demonstrated in previous study by (Askar et al., 2011) who performed a study included 240 healthy women with viable normal singleton pregnancies achieving normal vaginal delivery at or beyond 37 weeks' gestation at Al-Azhar University hospital. There was a statistically highly significant difference in the estimated mean blood loss between the carbetocin and syntometrine groups, with a blood loss of 81.5 ml higher in the syntometrine group. The mean drop of hemoglobin concentration 24 h after delivery was 0.8 g/dl in carbetocin group and 1.1 g/dl in syntometrine group, and the difference was statistically highly significant.

There were no significant differences in the number of women with major PPH (blood loss >1000 ml) or number of women requiring blood transfusions. Hysterectomy for intractable postpartum hemorrhage occurs in one patient in Oxytocin & ergometrine group. However, this agree with (Attilakos et al., 2010)in his Double-blind randomised single centrestudy, his results showed that There were no significant differences in the estimated blood loss, uterine tone at the end of the operation, number of women with major PPH (blood loss >1000 ml) or number of women requiring blood transfusions.

Conclusion

This study concludes that intravenous carbetocin is effective to prevent atonic post-partum haemorrhage following cesarean section. It is as potent as combination of I.V syntocinon & ergometrine. In contrast with combination of syntocinon & ergometrine, carbetocin alone is one drug with less maternal adverse effects like elevated blood pressure, nausea and vomiting.

The use of additional uterotonic drugs is less in carbetocin group than in syntocinon & ergometrine group.

Carbetocin is associated with less blood loss than syntocinon & ergometrine. It is also associated with fewer dropsin postoperative hemoglobin level.

Acknowledgement

I would like to express my deep gratitude and thanks for Professor Dr. Ihab Hassaneen (Professor of Obstetrics and Gynecology) for supervising and completion of this work.

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5/25/2016