Carbetocin versus oxytocin combined with misoprostol for prevention of postpartum hemorrhage in patients with severe pre-eclampsia: A randomized control trial

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Abstract

Background: Oxytocin is a uterotonic medication that promotes increased uterine tone and contractions, and is commonly administered immediately following delivery of the infant's shoulder as part of AMTSL. An alternative to oxytocin is misoprostol (Cytotec), an inexpensive medication that does not require injection and is more effective than placebo in preventing postpartum hemorrhage. Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single dose injection in the route of intravenous or intramuscular.

Aim of work: To compare the effectiveness of carbetocin alone versus oxytocin combined with misoprostol in prevention of postpartum hemorrhage in patients with severe pre-eclampsia.

Patients and methods: The study comprised 124 women with severe pre-eclampsia who underwent elective caesarean section, during the period from first of April 2020 to the end Marsh 2021.

Results: There was no statistically significant difference found between two groups regarding need for additional uterotonic, need for blood transfusion, need for instrumental currtage, oliguria and length of hospital stay, and there was statistically significant difference found between two groups regarding Hb difference, and there was highly statistically significant difference found between two groups regarding post partum Hb level. There was no statistically significant difference found between two groups regarding palpitation, fever, nausea, vomiting, hot sensation, fascial flushing and malaise, and there was statistically significant difference found between two groups regarding headache.

Conclusion: Carbetocin is superior than oxytocin combined with misoprostol in the prevention of postpartum hemorrhage in patients with severe pre-eclampsia recived magnesium sulfate to prevention of eclamptic fits.

Keywords: Carbetocin, Oxytocin, Misoprostol, Postpartum hemorrhage, Pre-eclampsia.

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Introduction

Postpartum hemorrhage (PPH) is a significant problem and a major cause of maternal mortality and morbidity, resulting in up to 28% of maternal deaths [1].

It can result from uterine atony, retained placental tissue including that from abnormal placentation, maternal genital tract trauma and coagulopathies [2]. Uterine atony is the major cause of postpartum hemorrhage (PPH), accounting for up to 80% of PPH cases [3].

Risk factors for PPH may be Suspected or proven placental abruption Known placenta Previa, multiple pregnancy, pre-eclampsia/ gestational hypertension, previous PPH, obesity, Anemia, delivery by elective caesarean section, induction of labour, retained placental tissues, prolonged labour and big baby [4].

Women with pre-eclampsia have a 1.53 fold increased risk for postpartum hemorrhage. Clinicians should be aware of this and use this knowledge in the management of pre-eclampsia and the third stage of labour [5]. Magnesium sulfate was used in 10% of the deliveries; however, preeclampsia is highly correlated with use of magnesium sulfate, magnesium sulfate in the setting of pre eclampsia may impair uterine contractility, resulting in uterine atony and hemorrhage. Because of its tocolytic effect [6].

Several uterotonics agents are used to prevent PPH because of uterine atony, including oxytocin, ergot alkaloid and prostaglandin [7].

Misoprostol is a prostaglandin E1 analogue with strong uterotonic properties and has been suggested as an alternative to inject able uterotonic agents for preventing PPH, It is cheap, heat stable, and can be administered through multiple routes [8].

Misoprostol has been widely recommended for the prevention of post-partum hemorrhage when other methods are not available. The most common regimen reported for the treatment of post-partum hemorrhage is rectally [9].

Carbetocin, a long-acting oxytocin analogue that bind to oxytocin receptors with higher affinity, its contractile effect of uterus are apparent within two minutes. A 100-μg dose of carbetocin has been recommended for preventing PPH in high risk patients. An advantage of carbetocin over others uterotonics is that, owing to its long half-life, it is administrated as a single intravenous dose [10].

The aim of this study was to compare the effectiveness of Carbetocin alone versus oxytocin combined with misoprostol in prevention of postpartum hemorrhage in patients with severe pre-eclampsia.

Patients and methods

In our case, acupuncture was effective in This a randomized control study comprised 124 women with severe pre-eclampsia who underwent elective caesarean section, was conducted at Department of Obstetrics and Gynecology, Aswan University hospital, during the period from first of April 2020 to the end Marsh 2021.

This study was divided into two equal groups: Group I: patient received 100 mcg of Carbetocin (Pabal) intravenous over one minute immediately after delivery of the baby, and Group II: patient received 10 IU oxytocin (Syntocinone) iv drip and 400 mcg of misoprostol rectally after anesthesia.

Randomization:

Randomization was done using computer-generated random table. Allocation concealment was ascertained using the serially numbered closed envelopes. After assessing the eligibility and obtaining the required consent, allocation of the patients was done by telephone of the primary center in Aswan University who had the serially closed envelops. Once allocation has been obtained, it could not be changed.

Inclusion criteria: Pregnant women which diagnosed with severe pre-eclampsia, singleton pregnancy, and termination of pregnancy by Cesarean section after 28 weeks of gestation.

Exclusion criteria: (High risk patients of post-partum hemorrhage). Suspected or proven placental abruption, known placenta Previa or acreata, multiple pregnancies, obesity (BMI > 35), anemia (< 9 g/dl), retained placental tissues, big baby (> 4 kg), presence of coagulopathy, polyhydramnios, presence of Uterine fibroids, medical diseases as; cardiac, liver, renal or endocrine diseases, general anesthesia, and longitudinal uterine incision.

All patients were subjected to:

- Detailed history taking.
- General examination.
- Abdominal examination.
- Investigation was done to confirm presence of sever pre-eclampsia.

The blood pressure was measured in a sitting position with an oscillometric device on the arm. We recorded the first blood pressure measurement in Medical Records before recruitment. After parturition, we recorded the blood pressure taken in the maternity ward after leaving the postpartum ward and contact with the participants (telephone, e-mail) was maintained.

The amount of blood loss was calculated according to number of soaked pads or dressing used after delivery for the 1st 24 hours. Where each soaked dressing = 50 cc. Intra-operative blood loss. Operative blood loss was calculated from the amount of blood in the suction bottle after delivery of placenta and the number of towels used and to which degree they were socked. Blood from the uterine incision, soaked towels and blood in suction bottle before placental delivery not added to the blood measurements.

N.B.: Soaked towel = 150 cc. Semi-soaked towel = 75 cc. The amount of blood loss was calculated according to number of soaked pads or dressing used after delivery for the 1st 24 hours. Where each soaked dressing = 50 cc.

Post-partum hemorrhage was considered:

- Minor PPH: if estimated blood loss is up to 1000 ml.
- Major PPH: if any estimated blood loss is over 1000 ml.

Clinical observation of patients was continued for the first 24 hours (every 10 minutes in first hour and then every hour for remaining 23 hours) for reporting and management of any degree of postpartum hemorrhage. The need for additional uterotonics agents (methyl-ergometrine, misoprostol) was recorded in both groups. The duration of the operation and blood transfusion, maternal pulse rate and fetal body weight was also recorded.

Follow up:

Intrapartum: Uterine tone. Further need for haemostatic measures will be also assessed. The occurrence of uterine atony requiring the use of additional uterotonics is considered the primary outcome of this study. The uterine tone was assessed by using a hand resting on the fundus and palpating the anterior wall of the uterus every two hours after the delivery.

Postpartum up to 24 hour: Uterine tone. Amount of vaginal bleeding. Hemoglobin level and hematocrit value, and the need for blood transfusion.

Ethical consent:

An approval of the study was obtained from Aswan University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 26. The qualitative data were presented as number

and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P value < 0.05 was considered significant.

Results

Table (1): Personal data of patients of both groups.

		Mean /N		SD/%	Median
		Carbetocin	Oxytocin plus misoprostol		
Age		29.3	29.3	5.82	29(25-34)
BMI		27.2	27.2	4.8	27(24-33)
Residence	Rural	26 (21 %)	25(20%)	6.8	
	Urban	36(29%)	37(30%)	7.2	

As regards the mean age of the participants in both groups was 29.23 years and the median was (25 – 34) years , The mean BMI of cases were 27.23 years median (24 – 33) (Table 1).

Table (2): Comparison regarding symptoms of severity of per-eclampsia in both groups.

		Carbetocin	Oxytocin plus misoprostol	P-Value	Sig.
		No.= 62	No.= 62		
Visual symptoms	No	52 (83.9%)	57 (91.9%)	0.169	NS
	Yes	10 (16.1%)	5 (8.1%)		
Epigastric pain	No	54 (87.1%)	53 (85.5%)	0.794	NS
	Yes	8 (12.9%)	9 (14.5%)		

There was non-statistically significant difference found between two groups regarding symptoms of severe PET (Visual symptoms and Epigastric pain) (Table 2).

Table (3): The incidence of PPH, Major PPH and Uterine atony in both groups after intervention.

		Carbetocin		Oxytocin plus misoprostol		P-value	Sig.
		No.	%	No.	%		
Uterine atony	No	55	88.7%	43	69.4%	0.008	S
	Yes	7	11.3%	19	30.6%		
PPH	No	56	90.3%	45	72.6%	0.011	S
	Yes	6	9.7%	17	27.4%		
Major PPH	No	62	100.0%	60	96.8%	0.154	NS
	Yes	0	0.0%	2	3.2%		

As regards the incidence of major PPH , this table shown that, there was no statistically significant difference found between two groups regarding Major PPH, and there was statistically significant difference found between two groups regarding PPH and Uterine atony (Table 3).

Table (4): Postpartum follow up for amount of blood loss in both groups.

		Carbetocin	Oxytocin plus misoprostol	P-value	Sig.
		No.= 62	No.= 62		
Amount of Bleeding	Mean ± SD	623.39 ± 267.15	792.74 ± 393.27	0.006	HS
	Range	300 – 1400	400 – 1900		
Need for additional utertonics	No	62 (100.0%)	60 (96.8%)	0.154	NS
	Yes	0 (0.0%)	2 (3.2%)		
Need for blood transfusion	No	62 (100.0%)	59 (95.2%)	0.080	NS
	Yes	0 (0.0%)	3 (4.8%)		
Oliguria	No	62 (100.0%)	61 (98.4%)	0.315	NS
	Yes	0 (0.0%)	1 (1.6%)		

As regards to the post-partum follow up, this table showed that, there was highly statistically significant difference found between two groups regarding amount of bleeding , and non-statistically significant difference found between two groups regarding. However, the need for additional uterotonic, and the need for blood transfusion showed that there was non-statistically significant difference found between two groups regarding oliguria (Table 4).

Table (5): Comparison regarding blood pressure and heart rate and blood haemoglobin level before and after delivery.

		Carbetocin	Oxytocin plus misoprostol	P-value	Sig.
		No.= 62	No.= 62		
Systolic bl. pressure	Mean ± SD	160.32 ± 7.51	159.03 ± 6.26	0.301	NS
	Range	150 – 180	150 – 170		
Diastolic bl. pressure	Mean ± SD	109.44 ± 7.02	108.23 ± 6.66	0.327	NS
	Range	100 – 120	100 – 120		
Systolic after delivery	Mean ± SD	127.90 ± 13.69	124.03 ± 11.66	0.093	NS
	Range	100 – 160	90 – 140		
Diastolic after delivery	Mean ± SD	83.29 ± 11.69	80.55 ± 16.35	0.285	NS
	Range	60 – 110	60 – 140		
Heart rate after delivery	Mean ± SD	88.85 ± 9.71	91.74 ± 12.18	0.147	NS
	Range	73 – 110	72 – 120		
Initial Hb level.	Mean ± SD	12.20 ± 0.70	12.30 ± 0.77	0.463	NS
	Range	10.6 – 13.7	9.5 – 13.9		
Postpartum Hb level	Mean ± SD	10.34 ± 0.61	9.95 ± 0.78	0.002	HS
	Range	8.8 – 11.3	8 – 11		
Hb difference	Mean ± SD	1.95 ± 0.83	2.35 ± 0.99	0.014	S
	Range	0.3 – 4.6	0.6 – 4.5		

There was non-statistically significant difference found between two groups regarding Systolic bl pressure and Diastolic bl pressure (before and after termination of pregnancy) and shows that there was non-statistically significant difference found between two groups regarding heart rate. There was non-statistically significant difference found between two groups

regarding initial Hb. level. However, it shows that, there was highly statistically significant difference found between two groups regarding post-partum Hb level. Also, it shows that, there was statistically significant difference found between two groups regarding HGb level difference pre and post-delivery (Table 5).

Table (6): Postpartum hospital stay and ICU admission in both groups.

		Carbetocin	Oxytocin plus misoprostol	Sig.
		No.= 62	No.= 62	
Length of hospital stay	Mean ± SD	3.21 ± 0.45	3.27 ± 0.45	NS
	Range	2 – 4	3 – 4	
Need to ICU due to sever PET	No	54 (87.1%)	57 (91.9%)	NS
	Yes	8 (12.9%)	5 (8.1%)	NS
Need to ICU due to other cause	No	59 (95.1%)	60 (96.7%)	NS
	Yes	3 (4.9%)	2 (3.3%)	NS

This table shows that, there was non-statistically significant difference found between two groups regarding length of hospital stay and Need to ICU admission (Table 6).

Table (7): Comparison regarding common side effects of both groups.

		Carbetocin		Oxytocin plus misoprostol		Test value*	P-Value	Sig.
		No.	%	No.	%			
Headache	No	58	93.5%	62	100.0%	4.133	0.042	S
	Yes	4	6.5%	0	0.0%			
Palpitation	No	62	100.0%	60	96.8%	2.033	0.154	NS
	Yes	0	0.0%	2	3.2%			
Fever	No	62	100.0%	60	96.8%	2.033	0.154	NS
	Yes	0	0.0%	2	3.2%			
Nausea	No	60	96.8%	62	100.0%	2.033	0.154	NS
	Yes	2	3.2%	0	0.0%			
Vomiting	No	60	96.8%	62	100.0%	2.033	0.154	NS
	Yes	2	3.2%	0	0.0%			
Hot sensation	No	61	98.4%	62	100.0%	1.008	0.315	NS
	Yes	1	1.6%	0	0.0%			
Fascial flushing	No	61	98.4%	62	100.0%	1.008	0.315	NS
	Yes	1	1.6%	0	0.0%			
Malaise	No	61	98.4%	62	100.0%	1.008	0.315	NS
	Yes	1	1.6%	0	0.0%			

There was non-statistically significant difference found between two groups regarding palpitation, fever, nausea, vomiting, hot sensation, fascial flushing and malaise, and there was statistically significant difference found between two groups regarding headache (Table 7).

Discussion

As the primary outcome of our study was the amount of postpartum bleeding and the occurrence of PPH, there was highly statistically significant difference found between two groups regarding the occurrence of PPH as carbetocin group have less incidence with (P value 0.011) and there was statistically significant difference found between two groups regarding the occurrence of postpartum uterine atony (P value 0.008). on the other hand, there was none statistically significant difference found between them regarding the occurrence of major PPH.

In agreement of our study, Ali et al. [11] showed that the incidence of postpartum hemorrhage was less in carbetocin group as they found in 6% (3 cases), 14 % (7 cases) and 12% (6 cases) in Carbetocin, Oxytocin and Misoprostol groups respectively. Also, they found that, the difference was moderately statistically significant, as regard to severity of postpartum hemorrhage as the incidence of major PPH was 0 (0%), 2 (4%) and 3 (6%) in Carbetocin, Oxytocin and Misoprostol respectively and the difference was highly statistically significant (P <0.0001) so , they concluded that, carbetocin was superior to oxytocin and misoprostol in prevention of atonic PPH in high-risk patients underwent elective caesarean section delivery and they recommend the use of carbetocin for all cases undergoing elective caesarean section and carry a risk factor for postpartum hemorrhage.

In Ali et al. [11], study, all the uterotonics were used separate but in our study, we use the combination between the oxytocin and misoprostol and still the carbetocin group have less incidence of PPH even if with the use of magnesium sulfate (tocolytic as a preventive measurement of convulsions in sever preeclampsia.

In our study findings were in agreement to what was reported by Dansereau et al.[12].

In accordance with our study, Larciprete et al. (13), reported 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

In the same way Attilakos et al. [14] study reported that, when carbetocin 100 μg and oxytocin 5 IU intravenously were compared for the prevention of PPH following cesarean section, there were significantly more women who needed additional oxytocics in the oxytocin group, while there were no significant differences in the estimated blood loss, uterine tone at the end of the operation, number of women with major PPH, number of women requiring blood transfusions, and the mean Hb fall after the operation.

Several studies discussed the efficacy of Carbetocin in prevention of postpartum hemorrhage during vaginal and cesarean deliveries. Boucher et al. [15] found that, a single dose of 100 μg of Carbetocin given with intravenous drip has been proved to be as effective as a 16-hour infusion of Oxytocin in prevention of intraoperative and postoperative blood loss after caesarean section.

Matching with our result, Chen et al. [16], they found in comparison the effect of Carbetocin prophylaxis in vaginal and CS that, a significant decrease in blood loss was noted with the prophylactic use of Carbetocin in cesarean deliveries.

Another study by Borruto et al. [1] were found that a single dose of Carbetocin had the same efficacy compared to two-hour Oxytocin infusion in prevention of intraoperative blood loss after removal of placental

An interesting result obtained in our study was finding that, there was none statistically significant difference found between two groups regarding need for additional uterotonic, need for blood transfusion, need for instrumental curettage, oliguria and length of hospital stay.

In the same way Ali et al. (11) study reported that, the needed for additional uterotonic agents and or for further surgical hemostatic measures were statistically significant lesser in Carbetocin group compared to the other two groups (oxytocin and misoprostol). These findings were in accordance with Borruto et al. (1) and Larciprete et al. [13].

Similarly, Fekih et al. [17] reported that a combination of misoprostol 200 μg with oxytocin has been demonstrated to reduce blood loss and the need for additional uterotonics.

But there was statistically significant difference found between two groups regarding Hb difference before and after the delivery which was less in carbetocin group with (P value 0.014).

Also, there was highly statistically significant difference found between two groups regarding postpartum serum Hb level which was higher in carbetocin group with (P value 0.002)

In disagreement with our results, El Sharkwy [18] reported that, in comparison of the combination of sublingual misoprostol and oxytocin infusion with intravenous carbetocin in the prevention of PPH during cesarean delivery in high-risk patients, they concluded that, both groups as effective as in reducing the need for additional uterotonic. These results in high-risk patient not in patients received tocolytic drugs before and after delivery as magnesium sulfate.

Also, El Sharkwy [18] concluded that in low-income countries, addition of a relatively tolerable small dose of sublingual misoprostol before CS managed by intravenous oxytocin can be a suitable substitute for the costly use of carbetocin in prevention of PPH in patients with risk factors. But in Egypt, the misoprostol not available in pharmacies and more expensive than carbetocin.

Conclusion

Carbetocin is superior than oxytocin combined with misoprostol in the prevention of postpartum hemorrhage in patients with severe pre-eclampsia recived magnesium sulfate to prevention of eclamptic fits.

Recommendation

We recommend the use of carbetocin as uterotonic to prevent the PPH in high risk patient especially sever pre -eclampsia received magnesium sulfate.

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Discussion

As the primary outcome of our study was the amount of postp

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