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Comparison of Carbetocin with Ergometrine for the prevention of postpartum hemorrhage

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Abstract

Introduction: Postpartum hemorrhage (PPH) is the leading cause of maternal mortality and is mainly treated with contraceptive drugs. The aim of research was to compare Carbetocin versus Ergometrine in women who undergo caesarian section.

Methodology: A single blind comparative prospective study was conducted at the G.N.M.A. "Elena Venizelou". The sample of the study consisted of 100 women of interest, who were randomly assigned to receive either Carbetocin or Ergometrine. The majority of the sample had not had a caesarean section in the past. Hematocrit levels, platelet count, blood loss, side effects, and frequency of rescue therapy were compared between the 2 groups.

Results: The Carbetocin group had 52 interest rates and the Ergometrine group 48. There was a statistically lower blood loss in the Carbetocin group ($p = 0.035$). There were no statistically significant differences in hematocrit levels, platelet count, side effects and frequency of rescue therapy between the 2 groups ($p > 0.05$).The presence of a side effect was associated with greater blood loss ($p \leq 0,017$). The application of rescue therapy was associated with higher hematocrit levels before drug administration ($p = 0.005$) and greater reduction after administration ($p = 0.007$) as well as greater blood loss ($p < 0.001$).

Conclusions: Carbetocin resulted in statistically less blood loss compared to Ergometrine, and showed similar results in terms of side effects and the application of rescue therapy. More randomized clinical trials are needed to determine the appropriate choice of contraceptive drugs in women who undergo a cesarean section.

Introduction

Death due to pregnancy complications remains a major cause of premature mortality in women worldwide, with an estimated 500,000 women dying during pregnancy each year. The most common complication is postpartum hemorrhage (PPH) accounting for 10% of pregnancy-related deaths. The inability of the uterus to contract after fetal delivery accounts for 70%-80% of the cases, with placental retention and coagulation disorders being other common causes [1]. Although maternal mortality rates have reduced significantly in the developed world, PPH remains the main cause of maternal mortality, especially in low-income countries [2]. The World Health Organization (WHO) recommends active treatment of obstetric hemorrhage after fetal delivery, even in low-risk patients [3].

Obstetric hemorrhage can be prevented by using one of the existing uterotonic drugs (or a combination of these), as the administration of uterotonic agents, immediately after birth, reduces the incidence of PPH by 40%. Today, the main uteronic drugs are oxytocin, carbetocin, ergometrine, and misoprostol [4]. Oxytocin is the most commonly available and widely used uteronic agent. However, its use has some limitations (short half-life and an antidiuretic effect) [5,6]. Carbetocin is a synthetic oxytocin agonist with a fourfold duration of action which makes continuous intravenous infusion unnecessary [7]. Ergometrine is a second-line uteronic agent due to its side effects (hypertension, nausea, vomiting) [8]. Misoprostol is characterized by low cost, high availability, minimal side effects and ease of administration, but recent research calls into question its effectiveness as an uteronic drug [9].

Although there are numerous reviews addressing the use of uterotonic agents in preventing PPH [10-13], a head-to-head comparison of ergometrine versus carbetocin has not been studied in women undergoing cesarean section. Moreover, since uterotonic agents, have rare but noticeable side effects on women in labor (drowsiness, nausea and vomiting) and their baby (short-term shortness of breath and drowsiness) [14], the

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present study compares carbetocin with ergometrine for the prevention of PPH, at women undergoing caesarean section with no increased risk of hemorrhage. Our aim was to record differences (if any) between carbetocin and ergometrine in hematocrit levels, platelet count, gauges weight before and after delivery, side effects, and rescue therapy.

Patients and Methods

Design

A prospective comparative single blind randomized study was conducted at the "Elena Venizelou "General Hospital, in Athens, Greece from October 2018 to December 2019. The study was approved by the Institutional Review Board of our Hospital, as it was found consistent with the Helsinki Declaration. Written informed consent was obtained from all participants, before enrollment. The trial was registered in the US National Library of Medicine registry.

Population-Sample

The study population (n=100) consisted of women that underwent cesarean delivery and were put into the ergometrine (n=48) and the carbetocin group (n=52). Exclusion criteria included (i) age below 18 or above 40 years, (ii) multiple pregnancies, (iii) abnormal placental adhesion, (iv) 2 or more cesarean sections in the past, (v) women with hematological diseases on anticoagulant treatment, (vi) cesarean section under general anesthesia and (vii) women who refused to sign a consent form.

Process

Deliveries were carried out by different obstetricians. A web-based system was used for allocation and data collection. Patients were assigned to either the ergometrin or the carbetocin group via computer-generated numbers using block randomization in a 1:1 ratio. A sealed envelope was handed out to the obstetrician, by a staff member with no participation in the study, allocating the patient to either one of two groups. That there is a rescue treatment in case of failure of the medication that will be given to them. Then, a complete history was taken and the standard laboratory test was performed, which included a general blood test, clotting times, biochemical test and cardiological evaluation.

Local anesthesia (dorsal, combined or epidural) was performed. After fetal ejaculation and placental abruption, the ergometrine group received 0.2 mg of ergometrine in a slow single infusion, while the carbetocin group received 100 mcg of carbetocin in 100 ml N/S 0.9% in a rapid intravenous drip infusion flow.

The efficacy of the treatment (loss of blood) was assessed by differences in the hemoglobin and hematocrit count (before and 24 hours after the end of the caesarean section), as well as from differences in intraoperative blood loss (calculated by weighing the gauzes and compresses before and after the operation), from the amount of blood collected in the suction bag and from any blood in the environment of the surgical bed area [15].

In cases where it was deemed necessary, rescue therapy was administered, consisting of 15iu oxytocin in intravenous drip infusion in the ergometrine group and 0.2 mg ergometrine in slow bolus infusion in the carbetocin group as well as 3 tb misoprostol in both groups which were administered intravenously.

Statistical Analysis

Scale variables were presented with mean values and standard deviations, while nominal variables with frequencies and percentages. To test difference of mean values between 2 large independent samples (n≥30) the parametric independent samples t-test was used while for dependent samples the parametric paired samples t-test. The non-parametric Mann Whitney U test was used to test medians of 2 small independent samples (n <30) that do not follow the normal distribution. The normality was tested using the Shapiro Wilk test. The X2 independence test was used to check the dependencies of nominal variables. Analyses were performed with the SPSS statistics version 24.0 software package (SPSS Inc., Chicago, IL) and the level of significance was set at 0.05 [16].

Results

Population characteristics

Table 1 presents the demographic characteristics of the study population. Thirty-three patients [17 ((35.4%) in the ergometrine group and 16 (30.8%) in the carbetocin group] had one previous cesarean section. Statistically significant differences were found in anticoagulant treatment (p=0.028) and elevated liver enzymes (p=0.049).

Changes in Hct, Platelet count and weight of gauzes

The Hct decrease in the carbetocin group was lower, as well as the reduction inthe platelet count; however, these differences were not statistically significant (p=0.160 and p=0.528, respectively). A statistically significant difference of the mean values in the gauze change was found with the increase in ergometrine (M = 1.018) to be greater (t (92.956) = 2.142, p=0.035) than the increase in carbetocin (M=0.920).

Table 2 presents the results of the hematocrit, platelet and gauzes of the patients before and after the administration of the substance, in terms of the type of substance administered.

Table 3 presents the results forhematocrit, platelet and gauzes in groups of side effects where a statistically significant difference was found in gauzes before (U=457.5, p=0.006), gauzes after (U=457.5, p=0.006), and gauzes change (U=390.5, p=0.017), so that the value in patients who had side effect to be greater.

Table 4 presents the results for the substance administered to the sample with side effects and rescue therapy. The rescue therapy was less applied to the carbetocin group of study (13.50%) comparing with ergometrine group (22.90%) but the difference was not considered statistically significant(X2=1.512, p=0.219). The presence of a side effect was lower in carbetocin (9.6%) comparing with ergometrine group (20.80%), however the difference was not considered statistically significant (X2=2.464, p=0.177).

Discussion

PPH is responsible for more than 10% of deaths associated with pregnancy. Active treatment of obstetric hemorrhage after fetal delivery is necessary even in low-risk patients. PPH can be prevented by using one of the existing uterotonic drug such as oxytocin, ergometrine, misoprostol and carbetocin. Uterotonic drugs are an ingredient in the active management of the third stage of childbirth, as they are the only intervention that is consistently proven to be beneficial. Uterotonic drugs

Table 1. Study population characteristic and baseline laboratory values

Demographics	**Ergometrine (N=48)**	**Carbetocin (N=52)**	**p**
Age	30.08 (6.34)	31.44 (6.77)	0.304
Weight (kgs)	74.13 (4.40)	75.23 (4.16)	0.199
Previous Caesarean section	35.4% (N=17)	30.8% (N=16)	0.621
Thyroid disease under treatment	2.1% (N=1)	3.8% (N=2)	0.606
DM	6.3% (N=3)	7.7% (N=4)	0.778
Gestational DM	2.1% (N=1)	0% (N=0)	0.296
Hypertension	0% (N=0)	3.8% (N=2)	0.170
Gestational hypertension	0% (N=0)	1.9% (N=1)	0.334
Anticoagulant treatment	0% (N=0)	9.6% (N=5)	0.028
Elevated serum liver enzymes	0% (N=0)	7.7% (N=4)	0.049
Preeclampsia	0% (N=0)	1.9% (N=1)	0.334
Thrombocytopenia	0% (N=0)	1.9% (N=1)	0.334
β-thalassemia minor	2.1% (N=1)	0% (N=0)	0.296
IVF	0% (N=0)	3.8% (N=2)	0.496
Increased serum uric acid	4.2% (N=2)	3.8% (N=2)	0.935
Hydramnios	0% (N=0)	1.9% (N=1)	0.334
Oligamnium	2.1% (N=1)	0% (N=0)	0.296
Anemia	0% (N=0)	3.8% (N=2)	0.170
Intrauterine Residual Fetal Development	0% (N=0)	1.9% (N=1)	0.334
Hepatitis C	2.1% (N=1)	0% (N=0)	0.296
Placental detachment	0% (N=0)	1.9% (N=1)	0.334
Immunodeficiency	2.1% (N=1)	0% (N=0)	0.296
HPV infection	0% (N=0)	1.9% (N=1)	0.334
CRP in 72 hours	0% (N=0)	1.9% (N=1)	0.334

DM: diabetes mellitus; IVF: in vitro fertilization, HPV: human papilloma virus, CRP: C-reactive protein

Table 2. Independent samples t-test for hematocrit, platelet and gauzes in groups of substance

Variable	Group	N	M	df	t	p
(Hct) before (x%)	Ergometrine Carbetocin	48 52	35.53 35.57	98	-0.069	0.945
(Hct) after (x%)	Ergometrine Carbetocin	48 52	31.93 32.8	98	-1.322	0.189
(Hct) change (x%)	Ergometrine Carbetocin	48 52	-3.6 -2.77	98	-1.146	0.16
(Plt) before	Ergometrine Carbetocin	48 52	235479.17 223500	98	0.931	0.354
(Plt) after	Ergometrine Carbetocin	48 52	214187.5 208173.08	98	0.499	0.619
(Plt) change	Ergometrine Carbetocin	48 52	-21291.67 -15326.92	98	-0.633	0.528
Gauzes before (Kg)	Ergometrine Carbetocin	48 52	0.399 0.368	89.169	1.252	0.214
Gauzes after (Kg)	Ergometrine Carbetocin	48 52	1.416 1.288	1.843	91.915	0.069
Gauzes change (Kg)	Ergometrine Carbetocin	48 52	1.018 0.92	2.142	92.956	0.035

M: Mean, df: Degrees of freedom, t: statistic of t-student

Table 3. Independent samples t-test and Mann Whitney for hematocrit, platelet and gauzes in groups of side effects

Variable	Side effects	N	M-M.R.	Statistics	p
(Hct) before (x%)	No	85	M=35.55	t (98) =-0.006	0.995
	Yes	15	M=35.55		
(Hct) after (x%)	No	85	M=32.42	t (98) =0.242	0.809
	Yes	15	M=32.19		
(Hct) change (x%)	No	85	M.R.=51.25	U=573.500	0.537
	Yes	15	M.R.=46.23		
(Plt) before	No	85	M.R.=48.96	U=506.500	0.206
	Yes	15	M.R.=59.23		
(Plt) after	No	85	M.R.=48.64	U=479.500	0.127
	Yes	15	M.R.=61.03		
(Plt) change	No	85	M.R.=51.04	U=592.000	0.66
	Yes	15	M.R.=47.47		
Gauzes before (Kg)	No	85	M.R.=48.38	U=457.500	0.006
	Yes	15	M.R.=62.50		
Gauzes after (Kg)	No	85	M.R.=47.59	U=390.500	0.017
	Yes	15	M.R.=66.97		
Gauzes change (Kg)	No	85	M.R.=47.59	U=390.500	0.017
	Yes	15	M.R.=66.97		

M: Mean, M.R.=Mean Rank, t: Statistic of t-student, U: Statistic of Mann Whitney

Table 4. X^2 test for side effects and rescue therapy in groups of substance

X2=2.464,p=0.177		**Side effects**	
		No	Yes
Substance	Ergometrine	79.2%	20.8%
	Carbetocin	90.4%	9.6%
Total		85.0%	15.0%
X2=1.512, p=0.219		**Rescue therapy**	
		No	Yes
Substance	Ergometrine	77.10%	22.90%
	Carbetocin	86.50%	13.50%
Total		82.00%	18.00%

reduce hemorrhage during and after labor, prevent changes in hemoglobin and hematocrit, and help control systolic and diastolic blood pressure [17].

However, the use of these agents creates side effects, so the search for the ideal uterotonic drug continues. The aim of the present study was to compare the effectiveness of carbetocin with ergometrine in preventing PPH in women undergoing cesarean section with no increased risk of hemorrhage. Identifying the most effective substance will determine the actions to be taken during cesarean section in order to prevent blood loss more effectively.

The survey involved 100 pregnant women, most of them Caucasians, average age 30-31 and weighing 74-75 kg. Of the 100 pregnant women participating in the study, 52 received carbetocin and 48 Ergometrine. The majority of the sample had not undergone a caesarean section in the past, nor had a severe medical condition in the past.

After the administration of the respective substance, the participants presented lower hematocrit. In particular, in the ergometrine group the decrease was 3.6 points while in the carbetocin the decrease was 2.77 points, with the difference not being considered statistically significant. In a similar study in 2016, there was no significant difference between the two study groups on hemoglobin and hematocrit at the beginning of caesarean section and after 2 days of surgery. However, the carbetocin group showed non-statistically significant but smaller rates of change than the ergometrine group [17]. Although the difference in HCt was not considered statistically significant, medically it can be considered important. Observing the changes, ergometrine resulted in a 0.83 higher decrease in hematocrit, which is medically important as

post-administration measurements of HCt were below 36%. Gabrielloni et al [18], even in normal childbirth, emphasize the need to maintain hematocrit values within normal limits, so that there is adequate oxygen transport and hemodynamics, resulting in small reductions (about 0.2%) to be considered harmful when the hematocrit is below 36%.

The reduction in platelets in the case of carbetocin (15.000) was smaller than the reduction in the ergometrine group (21.000), however this difference was not considered statistically significant. Similarly, in a 2016 study, the difference between the two groups, in terms of hemoglobin and platelets in postoperative measurement, was insignificant and had no clinical significance [19].

There was a statistically lower blood loss for carbetocin (0.920Kg vs. 1.018Kg), which highlights the increased potential of this drug in the treatment of PPH due to its increased duration of action. In a randomized study in 2018, which studied carbetocin versus the ergometrine-oxytocin combination, to prevent postpartum hemorrhage after cesarean section, 100 women received 100 micrograms of carbetocin, while another 100 received the combination of oxytocin 5 IU and I.M. ergometrine 0.2 mg after delivery. There was no significant difference between the two study groups regarding vaginal hemorrhage [20]. It is likely that the addition of oxytocin to the ergometrine balances the differences that would occur between carbetocin and ergometrine.

Ergometrine group had about twice many side effects (20.8% vs. 9.6%) comparing with carbetocin. However, the differences were not considered statistically significant. This highlights the potentially greater safety of carbetocin over ergometrine. However, the emergence of a side effect has been linked to greater hemorrhage, which is strange and difficult to explain and may be the subject of future research. Carbetocin is a synthetic oxytocin analogue. It combines the rapid onset of oxytocin with the long-term effect of ergometrine. Compared to oxytocin, it reduces the need for ruterototonic intervention with a similar frequency of side effects and, compared with the combination of oxytocin and ergometrine, is just as effective with fewer side effects, namely nausea, vomiting and hypertension [4].

The rescue treatment was applied less to the carbetocin (13.50%) interest rate group than to the ergometrine (22.90%), however the difference was not considered statistically significant. In a recent study [3], data for this comparison were obtained from a systematic review evaluating four trials (> 1000 women) examining carbetocin versus oxytocin-ergometrine combination. No significant difference was observed between the two groups in terms of postpartum hemorrhage, use of blood transfusion, or surgical treatment of PPH [3]. The addition of oxytocin to ergometrine balanced the differences between carbetocin and ergometrine.

Rescue therapy was associated with a lesser application after medication, as well as greater postpartum hemorrhage. This is to be expected, as in order for the rescue treatment to be applied the conventional treatment must have failed resulting in the possibility of reducing the hemorrhage. This highlights the effectiveness of each substance.

The general conclusion of the research is that the efficacy and safety of the drug carbetocin is similar to that of ergometrine. However, carbetocin resulted in statistically less blood loss. The disadvantage of carbetocin the high cost compared to that of ergometrine. This is due to the fact that carbetocin has not been established as the first substance of choice in the treatment of PPH. In a study conducted in 2018 at a hospital unit, which performs 12.000 per year with approximately 3.000 caesareans, the additional cost was estimated at $ 54.075 for the use of carbetocin [21].

Limitations-Suggestions

The results of the research can be generalized for Caucasian women of average age 30-31 years and weighing 74-75 kg, the majority of whom did not have a history of caesarean section and had no medical disease. However, the two groups of carbetocin and ergometrine differed significantly in anticoagulant therapy and liver enzymes, where higher values were indicated in the ergometrine group.In addition, in some cases, a small number of participants were identified, such as those who had side effects and patients who received rescue treatment, so that the parametric tests that are considered more reliable could not be applied. Similarly, a small number of participants were identified in the comparisons of the 2 groups in terms of medical history.

To strengthen the conclusions, future research with a larger sample which will have a complete balance between the 2 groups in the parameters of medical history and demographics is proposed, with a sample size that will be calculated from the size of the population.

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