Effect of carbetocin versus oxytocin On maternal blood loss following vaginal delivery: a double-blind ,controlled, randomized trial

Submitted For Partial Fulfillment of Master Degree in Obstetrics & Gynecology

By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

يَٰٓأَيُّهَا ٱلنَّاسُ إِن كُنتُمْ فِى رَيْبٍ مِّنَ ٱلْبَعْثِ فَإِنَّا خَلَقْنَٰكُم مِّن تُرَابٍ
ثُمَّ مِن نُّطْفَةٍ ثُمَّ مِنْ عَلَقَةٍ ثُمَّ مِن مُّضْغَةٍ مُّخَلَّقَةٍ وَغَيْرِ مُخَلَّقَةٍ
لِّنُبَيِّنَ لَكُمْ ۚ وَنُقِرُّ فِى ٱلْأَرْحَامِ مَا نَشَآءُ إِلَىٰٓ أَجَلٍ مُّسَمًّى ثُمَّ
نُخْرِجُكُمْ طِفْلًا ثُمَّ لِتَبْلُغُوٓا۟ أَشُدَّكُمْ ۖ وَمِنكُم مَّن
يُتَوَفَّىٰ وَمِنكُم مَّن يُرَدُّ إِلَىٰٓ أَرْذَلِ ٱلْعُمُرِ لِكَيْلَا يَعْلَمَ
مِنۢ بَعْدِ عِلْمٍ شَيْـًٔا ۚ وَتَرَى ٱلْأَرْضَ هَامِدَةً فَإِذَآ أَنزَلْنَا عَلَيْهَا
ٱلْمَآءَ ٱهْتَزَّتْ وَرَبَتْ وَأَنۢبَتَتْ مِن كُلِّ زَوْجٍۭ بَهِيجٍ ﴿٥﴾

صَدَقَ اللهُ العَظِيمْ

سورة الحج: آية (5)

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Mustafa Mahmoud Khattab

Protocol

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Protocol of Thesis

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Introduction

The third stage of labour is that period from delivery of the baby until delivery of the placenta. After delivery of the baby and cessation of umbilical cord pulsation the placenta separates from the uterine wall through the spongy lining of the (decidua spongiosa) and is delivered through the birth canal. The placenta separates as a result of capillary hemorrhage and the shearing effect of uterine muscle contraction.[1]

The degree of blood loss associated with placental separation and delivery depends on how quickly the placenta separates from the uterine wall and how effectively uterine muscle contracts around the placental bed (where the placenta is attached to the wall of the uterus) and the blood vessels, during and after separation, and expels the placenta through the birth canal. Moderate loss of blood is physiological and unlikely to lead to later problems except for women who are already anemic. The major complication associated with this stage is postpartum hemorrhage. This is not necessarily torrential bleeding, and is usually defined as bleeding from the genital tract of 500ml or more in the first 24 hours following delivery of the baby.[2]

Postpartum hemorrhage is the most common cause of maternal death worldwide. Most cases of morbidity and mortality due to post-partum hemorrhage occur in the first 24 hours following delivery and these are regarded as primary post-partum hemorrhage whereas any abnormal or excessive bleeding from the birth canal occurring between 24 hours and 12 weeks postnatally is regarded as secondary post-partum hemorrhage. Post-partum hemorrhage may result from failure of the uterus to contract adequately (atony), genital tract trauma (i.e. vaginal or cervical lacerations), uterine rupture, retained placental tissue, or maternal bleeding disorders. Uterine atony is the most common cause and consequently the leading cause of maternal mortality worldwide.[3]

According to the National Maternal Mortality Study conducted in Egypt in 2000 postpartum hemorrhage (PPH) alone was responsible for 27% of all maternal deaths, making it the leading contributor to maternal mortality in Egypt.[4]

Numerous factors lead to increased incidence of postpartum hemorrhage like prolonged labor, multifetal gestation, large baby, anemia, pre-eclampsia and operative vaginal deliveries. Although one or more risk factors may increase the chance of postpartum hemorrhage, two thirds of postpartum hemorrhage cases occur in women with known risk factors. Hence all pregnant women remain at risk for this catastrophic event.[5]

Complications of postpartum hemorrhage include orthostatic hypotension, anemia, and fatigue, making maternal care of the newborn more difficult. Postpartum anemia increases the risk for postpartum depression .[6]

Each year thousands of women die from post-partum hemorrhage around the world. The prevention and management of postpartum hemorrhage are therefore very important aspects of maternity care. Clinicians should identify risk factors, take steps to prevent post-partum hemorrhage and learn and employ as many of the management techniques as possible. [7]

Routine active management of the third stage of labour (AMTSL) has been recommended for vaginal deliveries in hospital settings. It involves prophylactic administration of utrotonic agents after delivery of the anterior shoulder, controlled umbilical cord traction an early cord clamping and cutting. A key aspect in prevention of post-partum hemorrhage is utrotonic therapy. The most widely used agent is parenteral oxytocin and / or ergometrine. [8-9-10]

Oxytocin, Ergonovine and Methylergonvine are all employed widely in the third stage of labour but the timing of their administration differs in various institutions. Oxytocin which is commercially available in the United States as syntocinon and Pitocin should be given as a dilute solution by continuous intravenous infusion or as intramuscular injection in a dose of 10 IU. In cases of post-partum hemorrhage oxytocin may be injected directly into the uterus either transvaginally or transabdominally.[11]

Prophylactic use of an oxytocin agent after delivery of the infant has been shown to reduce the incidence of PPH by 40%. The most common practice in United States for prevention of post-partum hemorrhage is intravenous oxytocin administration after placental delivery.[12]

Carbetocin, a new drug for the prevention of uterine atony, is a synthetic analogue of oxytocin with a half-life of up to 4 to 10 times longer than that of oxytocin. In comparison with oxytocin, it is used as a single-dose injection instead of an infusion and can be given intravenously or intramuscularly. The bioavailability is 80% after intramuscular injection, and the optimal dose used in the third stage of labor is 100 μg. In contrast, carbetocin (1-deamino-1-carba-2-tyrosine(O-methyl) oxytocin) is a synthetic oxytocin analogue that binds to the same oxytocin receptors in the myometrium with an affinity similar to that of oxytocin. Its main advantage over oxytocin is a four-fold longer uterotonic activity, a fact which precludes the necessity of a continuous infusion.[13]

Aim of the work

The Aim of This Work is To Compare between The Effect of Carbetocin versus Oxytocin given prophylactically in The Third Stage of Labour on Maternal Blood Loss following Vaginal Delivery.

Patients and Methods

118 pregnant women with the following selection criteria admitted at Ain Shams University Maternity Hospital will be chosen to participate in the study after obtaining an informed consent.

They will be divided into two groups:

Group A: will receive 10 IU of oxytocin by intramuscular injection after delivery of the anterior shoulder.

Group B: will receive a single 100 μg intramuscular dose of carbetocin after delivery of the anterior shoulder.

Inclusion criteria:

Pregnant women beyond 36 weeks' gestation with a viable fetus with at least one risk factor for post-partum hemorrhage achieving vaginal delivery will participate in the study. The post-partum hemorrhage risk factors which will be included in this study are:

a-A history of blood transfusion or iron sucrose injection pre or post delivery.

b- A history of retained placenta. c- Grandmultiparity (>para 5).

d- Twin pregnancy.

e- Fetal macrosomia (fundal height >40 cm or ultrasound estimated fetal weight 3.8– 4.0 kg).

f- Polyhydramnios (more than one amniotic fluid pocket >8.0 cm or amniotic fluid index (AFI) >25.0 cm).

g- Induction or augmentation of labor with oxytocin for at least 4 hours

Exclusion criteria

a- Women younger than 18 years.

b- Women with history of significant heart disease.

c- Hypertension requiring treatment.

d- Hypersensitivity to oxytocin or carbetocin.

e- A history or evidence of liver, renal, vascular disease or endocrine disease (excluding gestational diabetes).

- The patients will be monitored for side effects of the selected drug in the first 24 hours after delivery regarding:

1. Estimated mean blood loss.
2. Change in pre and post delivery hemoglobin (Hb) and haematocrit levels.
3. Maternal adverse drug reactions such as headache, vomiting, abdominal pain, pruritus, hypotension or hypertension.
4. Manual removal of the placenta.
5. Need for blood transfusion.
6. Use of additional therapeutic uterotonics.
7. Third stage of labour lasting more than 30 minutes.
8. Postpartum hemorrhage (PPH) (equal to or greater than 500 ml)
9. Severe PPH (equal to or greater than 1000 ml)

Data collection and analysis

*** Assessment of methodological quality**

We will extract information on participants, methods, interventions, outcomes, and results, and will evaluate the methodological quality then trial quality will be assessed.

The following features will be considered:

(a) Method of randomization.

(b) Method of allocation concealment.

(c) Blinding of participants, surgeons and outcome assessors.

(d) Completeness of follow up.

(e) Use of intention-to-treat analysis.

The allocation concealment of the study will be scored A (adequate), B (unclear), C (inadequate) or D (not used) according to the rating system.

Trials that were explicitly clear that there were concealment of allocation, blinding of outcome assessment and handling of dropouts and withdrawals with an intention-to-treat analysis were considered to be of high quality (Juni 1999).

*** Data collection and synthesis**

Data will be extracted and Presentation of statistical data will include the use of relative risks for binary data and weighted mean difference for continuous data then the results from the trial will be combined by calculating the pooled relative risks/weighted mean difference and their 95% confidence interval.

For assessment of heterogeneity we will apply tests of heterogeneity using the I2 statistic. If high levels of heterogeneity among the trial will be identified (exceeding 50%), we will explore it by prespecified subgroup analysis and performed sensitivity analysis.

***Risk of bias in the study:**

Overall, reporting of methodological quality in the trial will be fair.

(1) Randomisation and selection bias

The randomization process in general and concealment of allocation in particular are considered the most important and sensitive indicators that bias will be minimized in a clinical trial (Schulz 1995). All the studies will be randomized. Method of randomization will be by computer-generated numbers, adequate concealment allocation will be described in the trial.

(2) Blinding of outcome assessment

The trial will be appropriately blinded; the participants, outcome assessors and the staff administering the medication will be blinded to the intervention. So our study will be randomized double blind prospective clinical trial.

(3) Handing of losses and attrition bias

This means women who will be excluded from the study because they did not receive the study medication. Or those who will not be subsequently included in the primary efficacy analysis due to major protocol violations.

(4) Intention-to-treat analysis

Intention-to-treat analysis will be performed for analysis of the adverse symptoms or signs. And also analysis of the efficacy of the interventions.

Sample size calculation

Sample size calculation for this randomized controlled trial rendered 118 subjects (59 subjects in each group) based on 79% and 53% outcome in exposed and unexposed groups respectively according to Boucher et al ;2008 and mean difference 3.30 according to Lin-Lin Su1 et al 2009 . With at least 80% power at Two-sided 95% significance level and ratio of exposed／unexposed 1: 1.

Sample Size for Randomized Clinical Trial studies

Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	53
Percent of Exposed with Outcome:	79
Odds Ratio:	3.3
Risk/Prevalence Ratio:	1.5
Risk/Prevalence difference:	26

	Kelsey	**Fleiss**	**Fleiss with CC**
Sample Size – Exposed	53	51	59
Sample Size-Nonexposed	53	51	59
Total sample size:	106	102	118

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15

Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19

CC = continuity correction

As seen from this table there are 3 results in each group 53, 51 or 59 I took the last one because it is a protective one.

Randamization will be done by random calculator, computer-generated numbers obtained from Graph Pad software.

Randomization

Subject #	Group Assigned
1	A
2	B
3	A
4	B
5	A
6	A
7	B
8	B
9	A
10	B
11	B
12	B
13	B
14	B
15	A
16	B
17	A
18	B
19	A
20	A
21	A
22	B
23	B
24	A
25	A
26	A
27	A
28	B
29	B
30	A
31	B
32	A
33	A
34	A
35	A
36	A
37	A
38	B
39	A
40	A

Subject #	Group Assigned
41	B
42	B
43	B
44	A
45	B
46	A
47	B
48	B
49	B
50	A
51	A
52	B
53	A
54	B
55	A
56	A
57	B
58	B
59	B
60	B
61	A
62	A
63	B
64	B
65	B
66	B
67	A
68	A
69	A
70	B
71	A
72	A
73	A
74	A
75	B
76	B
77	A
78	B
79	B
80	B

Subject #	Group Assigned
81	A
82	B
83	B
84	A
85	B
86	B
87	B
88	B
89	B
90	B
91	B
92	B
93	B
94	A
95	A
96	A
97	A
98	A
99	A
100	B
101	A
102	A
103	A
104	A
105	A
106	A
107	B
108	B
109	A
110	A
111	B
112	B
113	A
114	B
115	A
116	A
117	B
118	B