Carbetocin versus oxytocin for the prevention of postpartum haemorrhage during caesarean section-A study of 100 cases in Combined Military Hospital, Momenshahi

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Abstract
Postpartum bleeding or postpartum hemorrhage (PPH) is often defined as the loss of more than 500 ml in vaginal delivery or 1,000 ml of blood in caesarean section within the first 24 hours following childbirth. It occurs more commonly in those who: already have anemia, obesity, multiple pregnancy, older than 40 years of age. It also occurs more commonly following caesarean sections, during medications are used to start labor, during the use of a vacuum or forceps. In the developing world about 1.2% of deliveries are associated with PPH and when PPH occurred about 3% of women died. Globally it occurs about 8.7 million times and results in 44,000 to 86,000 deaths per year making it the leading cause of death during pregnancy. In UK, during 2000–2002, PPH was the second most frequent cause of maternal death. Caesarean section is an agonized risk factor for PPH and the worldwide caesarean delivery rate is increasing It has been found that a hormone named oxytocin, plays an important role to stimulate the uterus to contract shortly after the baby is born. Another drug named carbetocin is also used to control postpartum hemorrhage. So, in this study our main objective to find most crucial and effective drug of PPH prevention by comparing effectiveness of carbetocin vs. oxytocin.

Keywords: Postpartum hemorrhage, caesarean sections, carbetocin, oxytocin.

Introduction
Postpartum haemorrhage (PPH) remains a major cause of maternal deaths worldwide, and is estimated to cause the death of a woman every 10 minutes[1]. The risk of postpartum haemorrhage is much higher for women, when they are undergoing caesarean section. In most cases, uterine atony is responsible for the occurrence of excessive bleeding during or following childbirth[6]. There are signs or symptoms of low blood volume for the condition to exist[8]. Initial signs and symptoms are; an increased heart rate, feeling faint upon standing, and an increased breath rate[7]. Primary postpartum bleeding is defined as blood loss in excess of 500ml following vaginal delivery or 1000ml following caesarean section in the first 24 hours following birth[2]. Secondary postpartum bleeding is that
which occurs after the first day and up to six weeks after childbirth\cite{3}. As more blood is lost the women may feel cold, their blood pressure may drop, and they may become restless or unconscious\cite{7}.

Figure 1: This figure shows normal postpartum condition with contracted uterus preventing hemorrhage (upper) and uterine atony allows hemorrhage to flow into the uterus (lower). Prevention involves decreasing known risk factors including procedures associated with the condition, if possible, and give the medication oxytocin to stimulate the uterus to contract shortly after the baby is born\cite{2}. Oxytocin is a peptide hormone and neuropeptide. It is normally produced by the paraventricular nucleus of the hypothalamus and released by the posterior pituitary and plays a role in social bonding, sexual reproduction in both sexes, and during and after childbirth\cite{9,10}. The administration of oxytocics after the delivery of the neonate reduces the likelihood of PPH and 10 IU oxytocin through slow intravenous injection is currently recommended for all caesarean sections. The use of additional oxytocin medication is common to arrest bleeding, or prophylactically if there are risk factors for PPH. It has been revealed that an additional 8-hour oxytocin infusion was used in more than 20% of caesarean sections in an adult.

Figure 2: Chemical structure of oxytocin with labeled amino acids and oxytocin injection. Carbetocin is compared with oxytocin produced a reduction in women who needed uterine massage and further uterotonic drugs for women having caesarean sections. Carbetocin is a synthetic analogue of human oxytocin with structural modifications that increase its half-life thereby prolonging its pharmacological effects. Two double-blind randomized trials compared 100 µg carbetocin (the licensed dose) with different combinations of oxytocin, bolus and infusion, following caesarean section. The first trial found that significantly more women needed additional oxytocic interventions in the oxytocin group. The second trial found no significant differences in the intraoperative blood loss. This study compared carbetocin directly with the currently recommended (and licensed) dose of oxytocin (10 IU) so the performance of this comparison in a double-blind randomized trial\cite{2}.
Objective
To compare the effectiveness of carbetocin and oxytocin, when they are administered during caesarean section for prevention of postpartum haemorrhage (PPH).

Methodology

Study design
- Double-blind randomized single centre study (1:1 ratio).

Setting
- The study took place in Combined Military Hospital-Momenshahi, Mymensining for one year May 2017 to May 2018.

Primary outcome
- The proportion of women in each arm of the trial that needed additional pharmacological oxytocic interventions.

Secondary outcome
- Estimated blood loss, difference in preoperative and postoperative hemoglobin, vital signs during and after the operation, uterine tone, incidence of blood transfusion and adverse effects.

Inclusion criteria
- Women with a singleton pregnancy undergoing elective or emergency caesarean section after 37 weeks of gestation.

Exclusion criteria
- Women with multiple gestation, placenta praevia and placental abruption were excluded because there is a higher risk of hemorrhage with these conditions and it was therefore felt to be inappropriate to recruit these women. Women undergoing caesarean section with general anesthesia were also excluded, because carbetocin is licensed for use with regional anesthesia only. Furthermore, we excluded women undergoing caesarean section at less than 37 weeks of gestation (likely to be emergency caesarean sections; a different smaller group from term pregnancies) and women having emergency caesarean section for fetal or maternal distress where, due to time constraints, it was not possible and/or appropriate to recruit or randomize.

Methods
- Women were randomized to receive either carbetocin 100 μg or oxytocin 10IU intravenously, after the delivery of the baby. Perioperative care was otherwise normal and use of additional oxytocic was at the discretion of the operating obstetrician. Analysis was by intention to treat. Primary outcome measurement of this study was the proportion of women in each arm of the trial that needed additional pharmacological oxytocic interventions.
Data collection

Demographic, pregnancy and postnatal data were recorded by the researchers on the study preformats. Data relating to the operation [indication, estimated blood loss, additional oxytocic(s) used, uterine tone and adverse effects] were recorded on preformats filled in by the operating obstetrician. Blood loss was estimated by the surgeon in the usual way (visual estimation, number of used swabs and amount of aspirated blood). Blood pressure and pulse readings were recorded on the anesthetic and recovery charts. Women were followed up to discharge from the hospital.[2]

Table 1: Demographic and other baseline data for the two study groups; data are presented as n (%), unless stated otherwise

| Variable                        | Carbetocin % (n = 50) | Oxytocin % (n = 50) |
|---------------------------------|------------------------|----------------------|
| Age, median (range)             | 32 (18-42)             | 32 (18-44)           |
| Parity Primiparous(%)           | 11 (22%)               | 15 (30%)             |
| Multiparous (%)                 | 39 (78%)               | 35 (70%)             |
| Previous caesarean section (%)  | 33 (66%)               | 31 (62%)             |
| Emergency caesarean section (%) | 23 (46%)               | 32 (64%)             |
| Previous PPH (%)                | 13 (26%)               | 12 (24%)             |
| Other risk factors (%) PPH      | 31 (62%)               | 27 (54%)             |
| One risk factor                 | 25 (50%)               | 21 (42%)             |
| Two risk factors                | 06 (12%)               | 06 (12%)             |
| Prolonged labour                | 13 (26%)               | 12 (24%)             |
| Birthweight (gm), mean (SD)     | 3391                   | 3470                 |

Table 2: Outcome data for the two study groups; frequencies and percentages shown unless stated otherwise

| Variable                        | Carbetocin % (n = 50) | Oxytocin % (n = 50) |
|---------------------------------|------------------------|----------------------|
| Additional oxytocic given       | 13 (26%)               | 39 (78%)             |
| ProstaglandinE2                 | 05 (10%)               | 07 (14%)             |
| Methergin                       | 06 (12%)               | 08 (16%)             |
| Oxytocin infusion               | 02 (4%)                | 24 (48%)             |
| PPH                             | 19 (38%)               | 29 (58%)             |
| a. Estimated blood loss (500-1000 ml) | 12 (24%)             | 20 (40%)             |
| b. Estimated blood loss >1000 ml | 07 (14%)               | 09 (18%)             |
| Women transfused with blood     | 02 (04%)               | 04 (08%)             |
| Haemoglobin (g/dl)              |                        |                      |
| before LUCS                     | 10.6                   | 10.3                 |
| after LUCS                      | 10.2                   | 9.6                  |
| Secondary PPH                   | 00 (0%)                | 02 (0%)              |
| Uterine tone on day 1, median (range) | 9 (5-10)              | 9 (7-10)             |
| Pulse beat/min                  | 100-110                | 70-100               |
| BP at 0 min (mm of Hg)          |                        |                      |
| Systole                         | 100                    | 120                  |
| Diastole                        | 60                     | 70                   |
| BP at 60 min (mm of Hg)         |                        |                      |
| Systole                         | 120                    | 120                  |
| Diastole                        | 70                     | 80                   |
| O2 saturation                   | 100%                   | 100%                 |
| Nausea/vomiting                 | 06 (12%)               | 20 (40%)             |
| Itching                         | 00 (%)                 | 00 (%)               |
| Flushing                        | 00 (%)                 | 03 (6%)              |
| Restlessness                    | 03 (6%)                | 12 (24%)             |
| Other complications             | 00 (%)                 | 00 (%)               |

Result

Recruitment and randomization took place between May 2017 – May 2018. A total of 100 women were randomized in the study and analyzed. Women had previous PPH and PPH risk factors and the proportions were almost similar between the two groups. Women in the study required additional oxytocics such as 13% of women in the carbetocin group and 39% of women in the oxytocin group. Therefore, Result of this study showed, significantly more women...
required additional oxytocics in the oxytocin group. The majority of these women had oxytocin infusion, which were administered over 8 hours. There were no significant differences in the secondary outcomes, including major PPH, blood transfusions and fall in hemoglobin. It could be said that, carbetocin is associated with a reduce use of additional oxytocics. Table 2 also summarizes the reported adverse effects of the two interventions. The adverse effect profile appears similar and there was no significant difference in the number of women affected by at least one adverse effect.

Discussion
Historical data from the UK shows that the major reduction in PPH deaths occurred between 1850 and 1920, at a time when Ergometrine was only sporadically available and in an impure format[^11]. Much of the reduction in PPH deaths occurred before the arrival of purified oxytocin and the use of prophylaxis that started in the 1940s. The natural history of PPH suggests that most atonic PPHs are self-limiting, and that atonic deaths are relatively rare. Although 10% of women have a PPH without prophylaxis, PPH deaths only occur in around 0.27% of women without access to health care (27% of deaths in low-resource settings are from PPH and the highest maternal mortality rates in the world are around 1000 per 100 000; this represents 270 per 100 000 or 0.27%). Of these deaths, most result from untreated placenta praevia, retained placenta, or massive abruption. In South Africa, where access to oxytocics is not universal, the most common causes of PPH death are bleeding associated with caesarean section (26.2%), uterine rupture (17.9%), abruptio placenta (16%), and retained placenta (9.0%). Only 6% of PPH deaths result from uterine atony[^12].

The results suggest that carbetocin may be a more potent then oxytocic, but it is unclear whether this will reduce the rate of PPH in particular major PPH. There was no significant difference in the estimated blood loss, although this can be imprecise, especially for blood loss more than 1000ml but blood loss 500-1000ml is significant as it is almost double in oxytocin group. Women in both groups had their haemoglobin checked on the first postoperative day and found difference .4gm/dl in carbitocin group and 0.6 in oxytocin group. All the previous studies of carbetocin demonstrated a lower rate of additional oxytocic usage, but no study (including this one) has demonstrated a significant difference in the rate of PPH, which is arguably a more important outcome.

Limitation
In this study a potential limitation was that the utilization of extra oxytocics was bizarrely high. In our study, over half of the extra oxytocic drugs were given for PPH prophylaxis given not increasing the dose of carbetocin. Because maximum dose of carbetocin is not known. All things considered Table 2 exhibits that carbetocin diminishes the utilization of extra oxytocics for PPH.

Conclusion
Notwithstanding enormous interest in maternal wellbeing administrations all through the world, PPH remains a noteworthy reason for maternal demise. The fast beginning and movement of PPH implies that great administrations are required on the off chance that we are to forestall PPH-related mortality and dismalness. The arrangement of uterotonic to all ladies is essential, and the accessibility of misoprostol will achieve ladies who don't something else approach wellbeing administrations. Be that as it may, late investigations recommend that the fundamental advantage of prophylaxis is a lessening in the rate of baby blues frailty, with the impact on maternal passing staying less certain. In women at generally safe, around 7% in carbitocin group and 9% in oxytocin group lose more than 1000 ml of blood regardless of prophylaxis. These ladies require quick access to life-saving PPH treatment and protect treatments. Be that as it may, the
danger of major PPH is considerably higher in those with placental abruption, placenta praevia, multiple pregnancy and these ladies are correspondingly more averse to react to oxytocics. Huge numbers of these ladies will require progressed PPH treatments or on the other hand save medications to counteract dismalness and mortality. The eccentrics of numerous PPHs implies that gifted birth chaperons should go to conveyances, have proper obstetric emergency treatment aptitudes and gear, and the capacity to exchange ladies quickly. On the off chance that real enhancements in PPH-related mortality are to be accomplished, there should be an expanded arrangement of amazing crisis obstetric care administrations. This incorporates the arrangement of careful administrations to avoid PPH during caesarian section PPH therapeutic medicines, physical medicines (uterine pressure, tamponade, surgical medical procedure), and safeguard bundles (blood transfusion and blood items). More research is currently required to decide the most practical method for giving these administrations.

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