**Comparative efficacy of carbetocin and oxytocin in parturient at risk of atonic postpartum hemorrhage undergoing elective cesarean delivery: a multicentric randomized controlled trial**

**Background**: Postpartum hemorrhage (PPH) is a potentially life-threatening complication and one of the leading causes of maternal mortality. It has been estimated that one in every five maternal deaths occurs due to PPH globally. Maternal morbidity in the form of blood transfusion and hysterectomy rates has shown an upward trend even in the developed world. Primary PPH is predominantly caused by uterine atony or inadequate contraction of the uterus after childbirth. Active management of the third stage of labor involves prophylactic administration of a uterotonic agent prior to delivery of the placenta, as well as delayed cord clamping and controlled traction of the umbilical cord. The uterotonic administration remains the most essential component in terms of preventing PPH.

Oxytocin is the most commonly used first-line uterotonic. However, it loses its efficacy at room temperature and the logistic challenges to maintain proper cold-chain maintenance, especially in middle and low-income countries are prohibitive. Carbetocin, a long-acting, synthetic analog of oxytocin with a similar mechanism of action and is stable at room temperature for a longer duration, has also been proposed as a first-line drug for PPH prevention. Both these agents have a primary effect on oxytocin receptors in the uterus, however, their adverse effects are mediated by their actions on oxytocin receptors located in other tissues including cardiovascular system.

Most of the trials and larger meta-analyses evaluating the prophylactic role of oxytocin and carbetocin have focused on the low-risk PPH population. The incidence of biological risk factors for uterine atony such as advanced maternal age, multiple gestation (due to assisted reproductive techniques), and obesity has progressively increased in developed countries. A few small-sized trials evaluating the comparative efficacy of oxytocin and carbetocin in high-risk patients were very heterogeneous in their definition of the high-risk population. There

was also a huge variation in the dose, route, and mode of oxytocin administration in the trials. The adverse effects of oxytocin and carbetocin are influenced by the dose and route of administration. A recently published article on refractory uterine atony has recommended an intravenous bolus of oxytocin 3-5 IU over 1 min, followed by a maintenance infusion of 8–16 IU/h for 4 hours as a first choice for a high-risk for atonic PPH and intrapartum delivery and carbetocin 100 mcg intravenous over 1 minute was proposed as an alternative to oxytocin.[13]

**Objective**: The main objective of the study is to compare the efficacy and safety of intravenous administration of carbetocin 100 mcg with oxytocin bolus of 3 IU followed by continuous infusion of 250 mu/min over 4 hours in patients with biological high-risk factors for uterine atony in parturient undergoing cesarean delivery. We hypothesize that carbetocin will be superior to oxytocin with respect to our primary composite outcome.

**Design**: This will be a double-blinded prospective multicentre randomized controlled trial.

**Patients/Participants**: Adult parturients (>18 years) with term pregnancy (>37 weeks) with at least one risk factor for atonic postpartum hemorrhage undergoing cesarean delivery.

***Inclusion criteria****;*

1. Elderly parturient >40 years
2. Previous cesarean delivery
3. High parity (≥4 previous deliveries)
4. Overdistended uterus, due to

a) Polyhydramnios (AFI>24 cm)

b) Fetal macrosomia reported on prenatal ultrasound >90th centile or > 4000 gm

c) Multiple gestation

5. History of uterine atony/PPH
6. High BMI >40 kg/$m^2$
7. Hypertensive disorders
8. Antepartum hemorrhage
9. Uterine fibroids

***Exclusion criteria****;*

1. Valvular heart disease, arrhythmias or heart failure
2. Hemodynamic instability before surgery
3. Bleeding disorders
4. Anemia
5. Allergy or sensitivity to oxytocin or carbetocin

**Intervention:** IV carbetocin 100 mcg administered over 1 minute followed by placebo infusion over 4 hours after the delivery of the fetus.

**Comparator:** IV oxytocin 3 IU followed by continuous infusion of 250mu/min over 4 hours

***Composite Primary Outcome***

1. PRBC transfusion in 24 hours,
2. Intraoperative QBL > 1000ml,
3. Hysterectomy,
4. Admission to the Intensive Care Unit

**Secondary outcomes**

Quantitative blood loss, uterine tone, uterine compressions suture, intrauterine balloon tamponade, admission to a higher care unit, and adverse effects, namely, hemodynamic changes, nausea, vomiting, headache, and flushing.

***Anesthesia protocol***

Spinal anesthesia will be performed in the sitting position using a 25- or 27-gauge Whitacre needle. A mixture of hyperbaric bupivacaine 12–13.5 mg, fentanyl 10-15 mcg, and morphine 100-150 mcg will be given intrathecally over 30 s. The women will then be positioned in the supine position with left uterine displacement achieved by placing a wedge under the right buttock. Blood pressure and heart rate will be recorded at 1-minute intervals until satisfactory sensory level is achieved and every 2.5 min thereafter. Systolic blood pressure will be targeted to be maintained within 10% of the baseline value with prophylactic intravenous boluses or continuous infusion of phenylephrine. Immediately after the delivery of the fetus, the study drug (diluted to 10 ml with normal saline) will be administered as an intravenous bolus over 1 min and the study infusion will be commenced. The study drugs will be prepared pre-operatively by the research coordinator based on randomization. The patient, anesthesiologist, and obstetrician will be blinded to the study drug and infusion administered. The obstetrician will be asked to perform uterine massage and to allow spontaneous delivery of the placenta by controlled cord traction rather than active manual extraction. Second-line uterotonics (methylergonovine, carboprost, misoprostol) would be employed in case uterine atony persists after the use of a first-line agent (oxytocin or carbetocin) is found to be ineffective as decided by the team in the operating room.

**Statistical Analysis Plan:**

- Intention-to-treat analysis
- Double-blind, randomized

- Composite primary outcome

***Questions for SOAP Research Network Members:***

1. Are the inclusion/exclusion criteria too inclusive or exclusive and do they properly define “high risk”?
2. Is a superiority protocol the most appropriate?
3. Are the constituents of composite outcome appropriate?
4. Should there be a subjective assessment of the hemorrhage or tone?