Efficacy of Oxytocin Infusion VersusTranexamic Acid Infusion in Controlling Blood Loss during Elective Lower Segment Caesarean Section Randomized Clinical Trial

Thesis

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Introduction

Cesarean delivery is defined as the birth of a fetus through incisions in the abdominal wall (laparotomy) and the uterine wall(hysterotomy). This definition does not include removal of the fetusfrom the abdominal cavity in the case of rupture of the uterusor in the case of an abdominal pregnancy. The word *caesarean* was derivedsometimes in the Middle Ages from the Latin verb *caedere, to cut.* The German term *Kaiserschnitt*-Kaiser cut-reflects this derivation ***(Cunningham et al., 2013).***

The rate of cesarean section has increased in both developed and developing countries in recent decades ***(Betran et al., 2007).*** It was estimated in 2010 that CS rate was 32% in United States ***(Menacker and Hamilton, 2010)*** and 42% in China ***(Mi and Liu, 2014),*** which are both considerably higher than World Health Organization's recommended proportion of 10 to 15%.

Delivery by CS is associated with more complications than normal vaginal delivery e.g. infection at the incision site and uterus, more blood loss with anemia or blood transfusion (1% – 6% need blood transfusion), possible injury to bowel or bladder, scar tissue inside pelvic region with blockage and pain, extended hospital stay and recovery time, future pregnancy complications such as placenta previa and placental abruption and complications for the baby such as low APGAR score and

possible fetal injury ***(American Pregnancy Association, 2013).*** In spite of the various measures to prevent blood loss during and after caesarean section, post-partum hemorrhage (PPH) continues to be the most common complication seen in almost 20% of the cases, leading to increased maternal morbidity and mortality ***(Gohel et al., 2007).*** It is regarded as the leading cause of preventable maternal mortality worldwide ***(WHO, 2012).*** Besides, PPH is related with the increased rate of blood transfusion ***(Ekeroma, 2009)*** and the occurrence of serious anemia ***(AbouZahr, 2013).*** In severe cases, CSmay result in major obstetrichemorrhage, hysterectomy, admission to an intensive careunit or maternal death ***(Gungorduk et al., 2010).***

In order to reduce maternal mortality and morbidity caused by bleeding it is important to reduce the maternal bleeding during and after lower segment cesarean section ***(Kambo et al., 2012).*** Medications, such as oxytocin, misoprostol, prostaglandin F2a, and methylergonovine have been used to control bleeding after CS ***(RCOG Guidelines, 2014).***

The guidelines of the Royal College of Obstetricians and Gynaecologists (UK) on caesarean section recommend a slow intravenous bolus dose of 5 IU of oxytocin after delivery of the infant ***(RCOG Guidelines, 2014).*** In a survey of obstetricians and anaesthetists in the UK, the use of an oxytocin bolus was standard treatment, although the dose varied between 5 IU and 10 IU **(*Wedisinghe et al., 2008).*** In settings where an oxytocin bolus is

used routinely, an additional infusion of oxytocin may be required if haemorrhage occurs. This practice has led some obstetricians to use an additional infusion of oxytocin on a selective or routine basis for high risk cases, despite a lack of evidence to support this practice ***(Sheehan et al., 2010).*** By contrast, an alternative practice in the United States recommends the use of an oxytocin infusion instead of a bolus dose. This approach may reflect concerns about the physiological effects of bolus oxytocin ***(ACOG 2006).*** Intravenous oxytocin has a short half life (4-10 minutes); therefore the potential advantage of an oxytocin infusion at caesarean section is in maintaining uterine contractility throughout the surgical procedure and immediate postpartum period, when most primary haemorrhage occurs ***(Attilakos, 2010).***

Another popular approach is to minimize perioperative bleeding through the prophylactic use of antifibrinolytic agents such as aprotinin, tranexamic acid and amino caproic acid ***(Tidsskr, 2000).***

Tranexamic acid (TXA), a synthetic derivative of theamino acid lysine, is an antifibrinolytic that reversibly inhibits the activation of plasminogen, thus inhibiting fibrinolysis and reducing bleeding. TXA may enhance the effectiveness of the patient's own hemostatic mechanism ***(Bolton et al., 2003).*** It has been used to reduce blood loss and the need for allogeneic blood transfusion in cardiac surgery, liver transplantation, and orthopedic surgical procedures, with variable results ***(Gleeson et al., 2014).*** It is inexpensive and

treatment would be considered highly cost effective in high, middle and low income countries ***(Guerriero et al., 2011).***

A Cochrane systematic review -published in 2010 - examined the use of TXA to prevent PPH. It identified 5 RCTs and included 2 of them in the meta-analysis, which covered a total of 453 women. The authors concluded that the available evidence, although it suggested that TXA decreases postpartum blood loss ***(Novikova and Hofmeyr, 2010).***

Aim of the Work

This study aims to compare efficacy of oxytocin infusion after oxytocin bolus and effectiveness of tranexamic acid infusion after oxytocin bolus in controlling blood loss during elective lower segment caesarean section.

Hypothesis:

- In women undergoing elective lower segment caesarean section, after IV oxytocin bolus, tranexamic acid infusion and oxytocin infusion may be equally effective in controlling blood loss.

Study objective:

- The primary objective is to compare efficacy of oxytocin infusion after oxytocin bolus and efficacy of tranexamic acid infusion after oxytocin bolus in controlling blood loss during elective lower segment caesarean section.

Research question:

- In women undergoing elective lower segment caesarean section, are tranexamic acid infusion and oxytocin infusion equally effective in controlling blood loss during elective lower segment caesarean section after IV oxytocin bolus for both?

Patient and Methods

Population:

- The study group includes 138 pregnant women who admitted at Ain Shams University Maternity Hospital to be delivered through elective caesarean section.

Study Settings:

- Delivery unit at Ain Shams University Maternity Hospital.

Study Design

- It's an interventional randomized controlled clinical trial which will be conducted at Ain Shams University Maternity Hospital over a period of six months from January 2017 to June 2017.

Inclusion Criteria:

- All legally adult pregnant women (18 – 38 years old), primigravida or multigravida without history of previous caesarean section, at term (37 – 42 weeks), with singleton pregnancies, booked for elective caesarean section.

Exclusion Criteria:

- Medical disorders involving the heart, liver, kidney or brain.
- Diabetes mellitus and hypertension.

- Blood disorders (e.g. coagulopathies, thrombocytopenia)
- Patients requiring blood transfusion due to anemia.
- Risk factors for uterine atony e.g. macrosomia, polyhydramnios and multiple pregnancy.
- Allergy to tranexamic acid or oxytocin.
- Placenta previa or placental abruption
- Previous major obstetric haemorrhage (>1000 ml) in previous deliveries.
- Known fibroid or adenomyosis.
- Women who received anticoagulant therapy.
- Severe preeclampsis.
- Uterine anomalies.

Written Consent:

- The subjects under the study will be informed about the study plan and possible adverse effects. Informed written consent will be taken from all included pregnant women and will be approved by local ethical committee.

Methodology:

Allocation and concealment: One hundred and fifty opaque envelopes will be numbered serially. In each envelope the corresponding letter which denotes the allocated group will be put according to the randomization table. The letter (**O**) represents group (A), the letter (**T**) represents the group (B) and the letter (**C**) represents the group (C). Then all envelopes will be closed and put in one box. When the first woman arrives, the first envelope will be opened and the woman will be allocated according to the letter inside. There is an increase of number of envelopes by 10% of sample size to compensate withdrawal bias.

Randomization: It will be done using computer generated randomization sheet using MedCalc. Version 13.

- **All pregnant women will be subjected to:**

- Careful and detailed history:

1. Personal history:

- It includes name, age, occupation, residence and special habits of medical importance.

2. Obstetric history:

- It includes the first day of last menstrual period for accurate estimation of gestational age and antenatal care.

3. Past history:

- It includes the history of any medical disorder or surgical history.

4. History of present illness:

- It includes the medical and surgical condition to define high risk pregnancy.

Examination of the pregnants:

1. General examination:

- It includes pulse, blood pressure, temperature and respiratory rate.

2. Abdominal examination:

- It include the Inspetion for (Uterus size, Scars, Fetal movements and Umbilicus) and the Palpation for (Fetal growth, Liquor volume, Multiple pregnancy, Fetal lie and Fetal presentation).

3. Ultrasound examination:

- Assess viability of pregnancy.

- Determine gestational age.

- Assess amniotic fluid volume.

- Investigations for:

1. Complete blood count
2. Prothrombin time
3. Activated partial thromboplastin time
4. Liver function tests
5. Kidney function tests

- **The cases that fulfill the criteria will be randomly distributed into three groups:**

- ***Group (A):*** 46 women were assigned to receive an intravenous slow bolus of oxytocin 10 IU over 1 minute after delivery of babyfollowed by 40 IU oxytocin in 500 ml of 0.9% saline solution over 4 hours.

- ***Group (B):*** 46 women were assigned to receive an intravenous slow bolus of oxytocin 10 IU over 1 minute and 1 gmtranexamic acid in 200 ml of 0.9% saline solution over 5 minutes after delivery of baby.

- ***Group (C);*** 46 women were assigned to receive only an intravenous slow bolus of oxytocin 10 IU over 1 minute after delivery of baby. It represented a control group.

- **Estimation of blood loss will be through two ways:**

(1) <u>Measuring blood loss:</u>

The amount of blood loss (ml) = [(weight of the used towels – weight of the towel prior to the surgery) + the volume sucked in the suction bottle after placental delivery in ml] provided that conversion of weight of towels by (gm) to volume by (ml) by equation (1000 gm = 962 ml) ***(Michael, 2004).***

Note: measuring blood loss will be after delivery of placenta and four hours postpartum after completion of LSCS and all pads will be included in the estimation.

(2) <u>Calculating blood loss:</u>

The amount of blood loss (ml) = [estimated blood volume × (preoperative PCV – postoperative PCV) / preoperative PCV]

(where estimated blood volume = booking weight (kg) × 85) ***(Carvalho et al., 2004).***

- Also, heart rate, respiratory rate and blood pressure will be checked before the surgery, immediately after placental delivery and one and four hours after birth, respectively. Hemoglobin and hematocrite values will be noted 24 hours after operation for all groups.

Outcome Criteria:

- The primary outcomes:

❖ Gravimetric assessment of "measured" blood loss by measuring the suction volume and swab weight and mathematical estimation of "calculated" blood loss.

- The secondary outcomes:

❖ Major obstetric haemorrhage defined as calculated blood loss > 1000 ml.

❖ Use of an additional uterotonic agent.

❖ Vital data during first four post operative hours (blood pressure and heart rate).

❖ Vaginal bleeding during first four post operative hours.

❖ 24 hours post operative hemoglobin and haematocrit.

❖ Maternal and neonatal side effects of oxytocin and tranexamic acid.

Statistical Methods:

- **Sample Size Justification:**

Sample size was calculated using STATA® version 11 program, setting the type-1 05 and the power (1-β) at 0.7. Results from a previous study showed that the mean loss was 583 ±189 for oxytocin, while it was 336±151 for tranexamic ***(Sharon et al., 2011).*** Calculation according to these values produced a minimalsample size of 45 cases in each group.

(Reference for program: *Stata Corp. 2001. Statistical Software: Release 7.0. College Station, TX: Stata Corporation).*

- **Data Management and Statistical Analysis:**

The collected data will be revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001)**. Data will be presented as Mean and Standard deviation (± SD) for quantitative parametric data, and Median and Interquartile range for quantitative non parametric data. Frequency and percentage will be used for presenting qualitative data.Suitable analysis will be done according to the type of data obtained. Student T Test or Mann Whitney test will be used to analyze quantitative data while chi square test and fisher exact test will be used to analyze qualitative data.