Introduction

Cesarean delivery is the most common major surgical procedure performed on women worldwide and its rates continue to rise steadily in both developed and developing countries***. (Gibbons. et al., 2012)***

Recent studies report an increase in the rate of postpartum hemorrhage, which has been attributed, at least in part, to a rise in the rate of cesarean delivery ***(Mousa et al.2009, Joseph et al., 2007).***

Large population- and hospital-based cohort studies have attributed this to uterine atony after vaginal or cesarean deliveries***. (Ford . et al.2007, Callaghan. et al.2010)***

Postpartum hemorrhage (PPH) is defined as a blood loss of more than 1000 ml in the first 24 h. following cesarean, and it is a leading cause of maternal mortality worldwide, with the number of maternal deaths due to postpartum hemorrhage is estimated to exceed 100,000 maternal deaths each year.***(Gibbons . et al.,2012)***

Recent studies have estimated that the prevalence of postpartum hemorrhage after cesarean delivery ranges from 0.6% to 6.4% (median, 3%). ***(Bateman. et al. 2010, Skjeldestad, Am J Obstet Gynecol. 2012)***. The efficacy of routine administration of uterotonic agents to reduce the frequency of postpartum hemorrhage after vaginal birth is well-established***. (NICE clinical guideline.2011)***

Misoprostol, is a synthetic prostaglandin E1 analogue with strong uterotonic properties, it has been suggested as an alternative to injectable uterotonic agents for preventing postpartum hemorrhage following deliveries, being now one of the most popular drugs in obstetrics ***(Mousa et al. 2009),*** and prophylactic administration of misoprostol after cesarean delivery is increasing nowadays to decrease blood loss after CS delivery.

The low cost of drug, safety, stability, and the ease of administration through multiple routes make it a good option in patients who are vomiting or under anesthesia ***(Derman et al., 2006),*** the drug was proved to be effective in reducing blood loss when administered orally, buccally, sublingually, vaginally and rectally in many previous studies***(Tang et al.2002, Picklu et al., 2010)*** .

A randomized controlled trial of preoperative misoprostol was conducted in a cohort of women scheduled for elective cesarean delivery, the study included 400 women, and showed the impact of preoperative rectal misoprostol on intra-operative blood loss during and after elective cesarean delivery by giving 400 μg of rectal misoprostol just before skin incision and the study come to result that rectal misoprostol was effective in reducing intra-operative and postpartum blood loss after elective Cesarean delivery managed by intravenous oxytocin***. (Elsedeek et al., 2012)***

Another systemic review and meta-analysis was conducted to evaluate the efficacy and safety of prophylactic misoprostol use at cesarean delivery for reducing intra-operative and postoperative hemorrhage. The meta-analysis included Seventeen studies (3174 women) of which 7 evaluated misoprostol versus oxytocin and 8 evaluated misoprostol plus oxytocin versus oxytocin. Rectal misoprostol, compared with oxytocin, was associated with a significant reduction in intraoperative and postoperative hemorrhage in contrast to sublingual or oral misoprostol and oxytocin where there were no significant differences in

intraoperative and postoperative hemorrhage. ***(Conde-Agudelo et al., 2013***)

Conde-Agudelo et al. mentioned in the implication of their research that further trials are still needed to show the effect of the combined use of misoprostol and oxytocin ,to determine the best route of administration , the optimal dose of misoprostol for reducing perioperative hemorrhage at cesarean delivery, the cost-effectiveness of this intervention, and the short- and long-term consequences of infants exposed to misoprostol in utero.

There is limited trials in that field of research in our country and this was the first trial comparing the effect of adding pre csrean section rectal misopristol with oxytocin versus placebo as regard the amount of intra-operative blood loss**.**

Aim of Work:

The aim of the this study is to compare between amount of intra-operative blood loss in women delivered by elective cesarean section who received preoperative rectally administered Misoprostol , and women delivered by elective cesarean section who did not receive any uterocolic drugs apart from stranded dose of oxytocin.

Question of the study:

In women delivered by elective cesarean section, Is there any difference in the amount of intra-operative blood loss between women received preoperative rectal misoprostol and women who received placebo (*oxytocin only without any further uterotonics*) as a part of active management of 3rd stage of labour?

Hypothesis of the Study:

In women undergoing elective cesarean section, rectal misoprostol may be effective as oxytocin in reducing intra-operative blood loss

Clinical trials identifier: NCT02509351

Methods: Participants, Intervention &Outcome

Study Setting:

This study will be conducted in the labor ward of Ain Shams University Maternity Hospital.

Trials design:

Parallel, superiority randomized controlled trial with allocation ratios 1:1. that will be conducted on pregnant

females (full term) (≥37 weeks) undergoing elective cesarean section.

Participants:

A total number of two hundred women all will deliver after 37 completed weeks of gestational age by elective C.S. They will be randomized (computerized based randomization) to preoperative rectal misopristol administration versus placebo (*no uterocolic drug administration apart from the standard dose,10 IU intravenous of oxytocin used in active management of 3rd stage of labour)* **Geen Top Guideline GTG , 52,**

All will be allocated to the study and are distributed into 2 groups, each group will include 100 women according to the following

Eligibility criteria:

***Inclusion criteria*:**

- Age 18 to 35 years old
- Pregnant women that completed 37 weeks of gestation.
- Scheduled for elective caesarean section.

***Exclusion criteria*:**

- Women in active labor.
- Known to have hypersensitivity to prostaglandins(PG).
- Women with associated medical illness with pregnancy (eg DM, hypertension or SLE)
- Women with a known coagulopathy problem.
- Pregnant women with abnormal placentation.
- Pregnant women with history of rupture uterus.

Intervention:

All patients will be* submitted to*:

- Complete history taking including personal history, present history, past history, menstrual history, obstetric history, medical history and family history.
- General, abdominal, and pelvic examination.
- Investigations in the form of: coagulation profile, Hb level and hematochrit 2 hours before C.S and after 24 hours of birth.
- patients under the study will be distributed in two groups.

- Group 1, includes 100 patients who will receive 400 mg of misoprostol rectally after anesthesia and urinary bladder catheterization (2 tablets each 200 mg)
- Group 2, will include 100 patients will receive placebo (only the routine 10 unites of oxytocin during cesarean section).
- All patients will receive 10 unites of oxytocin by intravenous infusion as done by routine standers during elective cesarean section (**GTG, 52**).
- Cesarean section will be performed by senior resident with adequate training (at least 2 years of experience) who is competent enough to perform operation with least complications.
- The estimation of blood loss will start from skin incision with dedicated nurse to be responsible for collection of blood and amniotic fluid in two separate suction sets and weighting surgical towels before and after the operation.
- Preoperative hemoglobin will be measured 2 hours before surgery and will be assessed 24 h after the operation.
- The total amount of the blood loss is calculated through the following formula:

  Blood volume= weight * avg blood vol. ***(Feldman JM. et al., 1995)***

Allowable loss=blood vol*In(initial Hct./Final Hct)

- Data will be collected and tabulated and statistically analyzed by to compare qualitative variables between groups.

Outcome:

Types of outcome measures:

Primary:

Intraoperative amount of blood loss in the 2 groups under the study.

Secondary:

1- Maternal:

- Total amount of blood loss in both groups (*according to the previously mentioned formula)*
- Hemoglobin level before C.S and after 24 hour of labor
- Post partum Hemorrhage(PPH), *defined as loss of 500 ml or more of blood from the genital tract within 24 hours of the birth of a baby, PPH can be minor (500–1000 ml) or major (more than 1000 ml). Major could be divided to moderate (1000–2000 ml) or severe (more than 2000 ml)* ***RCOG,GTG ,52***

- Need for blood transfusion
- Need for manual removal of placenta.
- Need of Additional uterotonics.
- Drug adverse effects as fever, vomiting, shevering, hypersensitivity reaction.

2- Neonatal:

- Apgar score (1 min, 5 minutes).
- Intubation.
- Serum bilirubin after24 hours of birth.
- Admission to special care nursery (SCN) or neonatal intensive care unit (NICU).
- Respiratory distress.
- Neonatal death.

Methods: Assignment of interventions (for controlled trials) Allocation:

Sequence generation:

- Randomisation will be performed in advance by computer using variable blocks the random number generator in MS Excel (Microsoft, Seattle, WA, USA)Randomization will be conducted by Alasdikaa centre (the centre responsible for the study coordination)

Allocation concealment mechanism:

- Sealed opaque sequentially numbered envelopes that contained the assigned intervention will be used to conceal the allocation. The envelopes will be placed in a box from which only 1 envelope could be drawn at a time. The staff member responsible for the random generation and the allocation-concealment process was not involved in the recruitment phase of the trial

Blinding

- According to study design, all women giving birth participating in the study, the main investigator and the assessor will be blinded to the study.

Sample Size Calculation

- By using intaoperative maternal blood loss as a primary outcome, with reference to the literature, and using PASS version 14 sample size software, a sample size of 100 patient per each group was needed to deliver a study power of 90%, and Alpha n. 0.05.(***Elsedeek et al.2012, Abd-Ellah et al. 2013)***

Statistical Methods:

- Data will be tabulated and analyzed using SPSS 19 statistical analysis package software.Normally distributed numerical data will be presented as mean ± SD, and skewed data as median and interquartile range. Qualitative data will be presented as number and percentage. Comparison of normally distributed numerical data will be done using the unpaired Student t test. Skewed data will be compared using the Mann-Whitney U test. Categorical data will be compared using the chi-squared test or Fisher's exact test, when appropriate. A two-sided p-value <0.05 will be considered statistically significant.

Ethical and legal aspect:

- After approval of the ethics committee, an official permission will be obtained from director and head of Obstetrics & Gynecological Department at Ain Shams the Maternity University Hospital, The significance and purpose of the study was explained to each woman participating in the study. Confidentiality of any obtained information was ensured to them.

Delegation of investigator responsibilities:

The investigator will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, their trial-related duties and functions. The investigator will maintain a list of sub-investigators and other appropriately qualified person to home he / she has delegated scientific trial-related duties.

Patient information and informed consent:

Before being admitted to the clinical study, the patient must sign a consent to participate after the nature, scope, and possible consequences of the clinical studies has been explained in a form understandable to here.

An informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient. After reading the informed consent document, the patient must give consent in writing. the patient`s consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions. If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must

take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by local legally recognized.

Alternative (e.g., the patient`s thumbprint or mark) the witness and the person conducting the informed consent discussion must also sign and personally date the consent document.

The original signed consent document will be retained by the investigator. The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

Confidentiality:

Only the patient number and patient initials will be recorded , and if the patient`s name appear in any other document (e.g., pathologist report), it must be kept in privacy by the investigator. The investigator will maintain a personal patient identification List (patient numbers with the corresponding patient named to enable records to be identified.