Rectal Misoprostol Versus Intravenous Oxytocin Infusion during Cesarean Delivery to Reduce Intraoperative and Postoperative Blood Loss

Thesis
Submitted for partial fulfillment of Master Degree
in Obstetrics and Gynecology

By

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Protocol

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INTRODUCTION

Postpartum hemorrhage (PPH) is a leading cause of maternal mortality and morbidity, especially in low-resource countries. The incidence of cesarean delivery is increasing, and the average blood loss during cesarean delivery (1000 mL) is double the amount lost during vaginal delivery (500 mL) **(*Magann EF*, 2005).** The hematocrit falls by 10% and blood transfusion is required in 6% of women undergoing cesarean delivery compared with 4% of women who have a vaginal birth ***(Combs CA, 1991).***

In developing countries, it is responsible for an annual mortality of approximately 150.000 women per year. In Egypt, it accounts for 24% of the causes of maternal deaths ***(Egyptian Ministry of Health, 1994).***

In 2005, there were an estimated 535.900 maternal mortalities in the world; 99% occurred in less developed nations where women are more vulnerable to adverse outcomes due to poverty, malnutrition and lack of access to healthcare service. Moreover, PPH can exacerbate existing anemia (Hemoglobin B 11.0 g/dL) leading to severe anemia (Hemoglobin B 7.0 g/dL) and is associated with significant long-term morbidity ***(NFHS-3, 2005-2006 & Maharaj D, 2007).***

Though many obstetric units use intravenous bolus or infusion of oxytocin to prevent uterine atony and blood loss during and after cesarean delivery, 10%–40% of women receiving oxytocin require additional uterotonic agents ***(Acharya G, Munn MB, 2001).***

Although oxytocin is considered a safe drug, it can cause tachycardia and hypotension, and it has negative inotropic, antiplatelet, and antidiuretic effects ***(Thomas JS, 2007).***

Misoprostol is an E_1 prostaglandin analog that can be taken orally,rectally, vaginally or sublingually. It doesn't need refrigeration and has a long shelf life. There have been over 30 randomized trials with more than 30.000 women assessing the efficacy of misoprostol for prophylaxis for the prevention of PPH **(WHO, 2009).** A meta-analysis of three randomized controlled trials (RCTs) at the community or primary health clinic (PHC) level ***(Derman RJ, 2006 & Hog L, Walraven G, 2005)*** showed a significant decrease in severe PPH: 2.3% vs 5.7% (3509 women; RR 0.59; 95% CI, 0.41–0.84) and concluded that misoprostol is useful where injectable uterotonics are not available ***(Alfirevic Z, 2007).***

Despite findings of the World Health Organization multicentre randomized trial and the recent Cochrane systematic review ***(Gulmezoglu AM, 2001)*** that injectable uterotonics are preferable to misoprostol for the routine active management of the third stage of labour in hospital settings, interest in misoprostol remains ***(Darney PD, 2001 & El-Refaey H, 2002),*** especially in developing countries. The ease of use and storage of misoprostol relative to parenteral oxytocics, as well as its low cost are the main attractions of misoprostol. These properties make misoprostol practical for use in home deliveries or by traditional birth attendants in less developed areas and may help reduce the relatively high rate of maternal mortality from postpartum haemorrhage in these areas. Since oral misoprostol was first suggested for use in the third stage of labour in 1996, there have been at least 21 randomized controlled trials conducted on this subject reflecting the importance placed on the use of misoprostol for preventing postpartum haemorrhage ***(El-Refaey H, 1996).***

In a pharmacokinetic study ***(Khan RU, 2003),*** rectal administration of misoprostol was found to be superior to oral administration for management of the third stage of labor, and rectally administered misoprostol has also been used with promising results for the prevention and control of PPH after vaginal births ***(Nasr A, 2009 & Parsons SM, 2007).*** Sublingual ***(Vimala N, 2006)***, oral ***(Lapaire O, 2006 & Zhao Y, 1998)*** and buccal ***(Hamm J, 2005)*** administration of misoprostol have been used for PPH prophylaxis during cesarean delivery. In one study, rectal misoprostol was used to treat established PPH after cesarean delivery ***(Lokugamage, 2001).***

The aim of the present study was to evaluate the efficacy and safety of rectal administration of 800 μg of misoprostol in preventing uterine atony and blood loss compared with intravenous infusion of oxytocin in Ringer lactate solution for routine use in cesarean deliveries.

1. PROTOCOL OUTLINE

1.1.Title:-

Rectal misoprostol versus I.V oxytocin infusion during cesarean delivery to reduce intraoperative and postoperative blood loss

1.2. Study Site:

Ain Shams University Maternity Hospital.

2. STUDY OBJECTIVES

2.1. Primary Objective:-

To compare the efficacy of rectal misoprostol with intravenous oxytocin infusion during cesarean delivery to reduce intraoperative and postoperative blood loss.

2.2. Secondary Objectives:-

a) Subsequent need of additional uterotonic drugs.

b) To document safety and evaluate adverse events recorded during the study either maternal or fetal.

3. STUDY DESIGN

It is an interventional prospective controlled study assessing the use of misoprostol rectally during cesarean delivery to reduce intraoperative and postoperative blood loss in comparison with routinely used intravenous oxytocin infusion.

3.1. Population:-

The population the Study will comprise 150 women undergoing elective cesarean delivery under general anaesthesia subjects included in the study will be randomized into 2 groups:

- **1st group** (75 women): will receive misoprostol (Misotac®, Sigma, Egypt) four tablets each 200 ug. Adminstrated rectally after induction of anaesthesia.
- **2nd group** (75 women): will receive 4 ampoules of oxytocin (Syntocinon®, Novartis) each contains 5 IU.of oxytocin after the delivery of the neonate over 30 minutes by iv infusion.

3.2. Study Treatment And Dosages:-

3.2.1. Test Drug (Manufactured by:Misotac®, Sigma, Egypt):- presentation: two strips each contain 10 tablets. Administration: 4 tablets rectally after induction of general anaesthesia**.**

3.2.2. Supplies and Accountability:

The investigators will deliver the study treatment only to patients included according to inclusion criteria described in the

protocol. The treatment will be provided by main investigators who will prepare the drugs.

3.3. Study Entry And Duration:-

3.3.1. Recruitment and Initial Assessment:

During the pre-selection visit, exclusion and inclusion criteria will be applied.

3.3.2. Sample Size Justification:

Regarding sample size, 150 women under going elective cesarean delivery under general anaesthesia

3.3.3. Study Duration:

The duration of the study is 1 year.

3.4. Selection of Patients:-

3.4.1. Subjects' recruitment:

The patients set for planned selective cesarean delivery will be approached to participate in this study. The study will be discussed with the patient and consent will be taken by the investigator involved with him.

3.4.2. Inclusion Criteria:

1- Age less than 40 years of age and more than 18years.

2- The gestational age between 37- 42 weeks

3- Primigravida or previous one section only

4- Singleton pregnancy

5- Elective cesarean delivery

3.4.3. Exclusion criteria:

1- Extreme of age (below18-above 40)

2- Two or more cesarean delivery

3- Polyhydraminous
4- Fetal macrosomia
5- Anemia Hb less than 8%
6- Severe pre eclampsia
7- Coagulopathey
8- Antepartum hemorrhage
9- Hypersensivitey to prostaglandins
10- Women with cardiovascular, respiratory, liver, heamatological disease

3.5. Data Collection And Schedule:-

3.5.1. Enrollment (recruitment) Data [Case Record Form (CRF) No. 1]:

Following admission, all patients will undergo complete clinical examination and detailed medical history will be obtained. Each patient will have a Case Record Form (CRF) in which the following data will be recorded.

- Patient initials.
- Previous deliveries and abortions Age, height, weight.
- Known allergies.
- Past medical and surgical history (no longer present).
- Medications taken within the last 4 weeks and discontinued.
- Concomitant illnesses.
- Clinical examination: including general, abdominal and vaginal.
- Indication of cesarean delivery.

- Ultra sound for amniotic fluid index.

3.5.2. Efficacy and Safety Data: [CRF No.2]:

3.5.2.1. Efficacy data

Will be recorded if decreasing intraoperative, postoperative blood loss, no changes in hematocrite value and no adverse effects.

3.5.2.2. Safety data

Spontaneously observed and reported adverse events, either maternal or fetal.

3.5.3. Special Situations Arising During the Treatment Period

Withdrawal upon patient's will:

The patient has the right to stop the treatment and to be withdrawn from the study without giving an explanation. In all cases, patients who will not fulfill the whole study observational period will not be replaced, but will be taken into account in the analysis of the intention to treat basis. Reasons for withdrawal will be recorded in the CRF and in the medical file of the patient.

3.5.4. Checkup Schedule:

Inclusion and follow-up visits will be run according to the schedule**:**

- **1st session:** Inclusion & exclusion criteria, examination**,** investigations(**complete blood picture).**
- **2nd session:** Hospital admission, Consent, clinical assessment
- **3rd session:** Intraoperative and postoperative assessment of ppH and side effects**.**

4. ETHICAL AND LEGAL ASPECTS

4.1. Good Clinical Practice (GCP):-

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the investigators abide by the principles of good clinical practice and the ethical principles laid down in the current revision of the Declaration of Helsinki.

4.2. 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, the study treatments, and their trial-related duties and functions. The investigator will maintain a list of sub-investigators and other appropriately qualified person to whom he or she has delegated significant trial-related duties.

4.3. Patient Information and Informed Consent:-

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to her. An informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient [Form 1]. 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 [Form 2]. Consent must be

confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (e.g., the patient's thumbprint or mark). The witness and the person conducting the informed consent discussions 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.

4.4. Confidentiality:-

Only the patient number and patient initials will be recorded in the CRF, and if the patients name appears on any other document, it must be kept in privacy by the investigators. The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

4.5. Protocol Approval:-

Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents will be declared for Ethical and Research approval by the Council of OB/GYN Department, Ain Shams University.

PATIENT INPUT FORM

Hospital Number	
Patient name	
Patient age	
Parity	
Gestational age	
Presentation	
Indication of cesearan section	
Aminuotic fluid index	
Approximate blood loss	
Estimated blood loss	
Blood transfusion	
Temperature	
Systolic and diastolic blood pressure	
Hb%	
Postpartum hemorrhage	
<u>Side effects</u> nausea ☐ **Vomiting Pyrexia** ☐ ☐ **Abdominal pain Diarrhe** ☐ ☐ **Headache Hot flushes** ☐ ☐ **Shivering Tiredness** ☐ ☐	
<u>Neonatal outcome</u> **Apgar score at one minute** **Apgar score at five minute**	

<u>Estimated blood loss</u>

Approximate blood loss (A) = a + [c - b]

a = volume of the contents of suction bottle

c = soaked towels

b = dry towels

Each 1 gm difference in weight between soaked and dry towels = 1ml

d = AFV (amniotic fluid volume) = AFI (amniotic fluid index) x 30ml ***(Lapaire O,Schneider MC.).***Int j Gynecol Obstet 2006

Estimated blood loss (B) = [A – d]

Postoperative bleeding over the next 8 hours was assessed by weighing the soaked pads and substracting the dry weight of pad.

Hb% and hematocrite was estimated 24 hours after the operation versus before the operation.

Statistical methods:

Data will be presented using percentages, means and standard deviation. Comparison of means will be done using a one-tail student's t-test. Comparison of percentages will be done using the chi-square test with continuity correction for small frequencies whenever applicable. All statistical calculations will be done using computer programs Microsoft Excel version 7 and SPSS (Statistical Package for the Social Science version 10.01) statistical program. A probability value (*P* value) less than 0.05 will be considered significant.

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