The Use of Buccal Misoprostol in Patients Undergoing Elective Cesarean Section

Thesis

Submitted for partial fulfillment of the master degree of ***in Obstetrics and Gynaecology***

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*First and foremost, I feel always indebted to **Allah**, the most kind and the most merciful.*

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Mohammed Sobhy

Contents

List of Abbreviations

ACOG	:	American college of obstetricians gynaecologists.
AR	:	Absolute risk.
ARR	:	Absolute risk reduction.
ASUMH	:	Ain Shams University Maternity Hospital.
Auc	:	Area under the curve.
BJOC	:	British journal of obstetrician and gynaeclogists:
BMI	:	Body Mass Index.
CBC	:	Complete Blood Count.
CEMACH	:	Confidential Enquiry into Maternal and Child Health
CI	:	Confidence Interval.
CMACE	:	Centre for Maternal and Child Enquiries.
CRF	:	Case record form.
DIC	:	Disseminated Intravascular Coagulopathy.
ERC	:	Ethics and research committee.
ICD	:	International Classification of Disease.
ICER	:	Incremental cost-effectiveness ratio
IQR	:	Interquartile range.
JNMC	:	Jawaharlal Nehru Medical College
MD	:	Mean difference.
MRI	:	Magnetic Resonance Imaging.
NICHD	:	National Institute of Child Health and Human Development
NNT	:	Number needed to treat.
OR	:	Odds ratio
PPH	:	Post Partum Hemorrhage.
RCOG	:	Royal College for Obstetricians and Gynaecologists.
RCT	:	Randomized Controlled Trial.
RR	:	Relative risk.

List of Abbreviations (Cont.)

SOGC	:	The society of obstetricians and gynaecologists of Canada.
UIC	:	University of Illinois Chicago.
UMKC	:	University of Missouri-Kansas City
WHO	:	World health organization.

List of tables

List of Figures

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A Protocol for Thesis

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INTRODUCTION

Postpartum hemorrhage (P.P.H.) is defined as loss of 500 ml or more of blood from the genital tract within 24 hours of the birth of a baby ***(Mousa and Alfirevic, 2007)*** but pre-existing health status like severe anemia or cardiac disease can make the effect of lesser blood loss life-threatening ***(Lalonde et al., 2006).*** It is potentially life threatening and a leading cause of maternal death worldwide ***(Li et al., 1996; McCormick et al., 2002; Lewis et al., 2007)*** *which is responsible for about one quarter of all maternal deaths worldwide* ***(Carroli etal.,2008)*** Uterine atony encounters for four-fifth of postpartum haemorrhage cases **(*Bouwmeester et al., 2005;* WHO, 2000), active** management of the third stage of labour using uterotonics during the vaginal delivery or caesarean section has successfully declined its occurrence ***(Chong et al., 2004*;Begley et al., 2010).**

The rate of postpartum hemorrhage increased from 1.5% in 1999 to 4.1% in 2009, and the rate of atonic postpartum hemorrhage rose from 1% in 1999 to 3.4%in 2009 ***(Lutomskiet al., 2012)***.

Oxytocin is the most widely used uterotonic agent ***(Bouwmeester et al., 2005; Wedisinghe et al., 2008)***, and has half-life of 4-10 minutes ***(Chard et al., 1970*)**. Prophylactic administration of oxytocin reduces rates of postpartum hemorrhage by 40 percent ***(Nordstrom et al., 1997*)**.

Administration of misoprostol have demonstrated lower efficacy than injectable uterotonic agents in preventing excessive bleeding following delivery ***(Gulmezoglu et al., 2004*)**.The peak concentration is achieved 30 minutes after sublingual and oral administration, whereas after vaginal administration, it takes 75 minutes ***(Tang et al., 2002*)** and in

rectal administration it takes 40-65 minutes ***(Meckstroth et al., 2006)***. It is associated with a high incidence of shivering, fever, and possible risk of severe hyperthermia **(Chong et al., 1997; Gulmezoglu et al., 2004).**

Injectable Oxytocin use lowered PPH in comparison to misoprostol, however prophylactic misoprostol significantly reduces PPH compared with expectant management in studies solely conducted in developing countries **(Gulmezoglu et al., 2004; Sloan et al., 2010).**

These factors deem misoprostol unsuitable for routine prevention of excessive postpartum bleeding in developed countries, despite low cost and ease of use ***(Gulmezoglu et al., 2004; Chong et al., 2005).***

Buccal administration of misopristol hasn't been extensively studied as other methods in the prevention of PPH. Only 2 studies encountered this with the use of only 200 Mcg. One of them related to the vaginal delivery ***(Bhullar et al., 2004)*** and the other concerned with caesarean section ***(Hamm et al., 2005)*** but non of them showed the superiority of misopristol to the intravenous oxytocin.

Buccal misoprostol has many advantages as it is away from the surgical field, and insures a continuous plasma level of a potent uterotonic agent ***(Tang et al., 2002)***

The 400-µg dose was chosen because maternal deaths have been reported in studies using more than 600 µg of misoprostol, whereas no difference in effect size was observed between the 400-µg and the 600-µg doses of the agent ***(Chong et al., 2005).***

Misoprostol was administered via the sublingual route,which is superior to oral and rectal administration ***(*Dansereau *et al., 1999)*** and is associated with rapid

absorption, prolonged duration of action, and the greatest total bioavailability when compared with other routes of administration.

Carbetocin is a synthetic analogue of human oxytocin with structural modifications that increase its half life; thereby prolonging its pharmacological effects ***(Sweeney et al., 1990)*** and is currently approved in 23 countries for prevention of uterine atony and excessive bleeding following caesarean delivery in spinal or epidural anesthesia ***(Rath et al., 2009).***

1. PROTOCOL OUTLINE

1.1 Title

The use of buccal misoprostol in patients undergoing elective cesarean section:

1.2 Study Site (Setting)

Ain Shams University Maternity Hospital (ASUMH) where there are approximately 15,000 deliveries per annum.

1.3 Study Phase

Phase III

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

To evaluate the efficacy of buccal misoprostol in the prevention of uterine atony and postpartum hemorrhage (PPH) after caesarean section in comparison to oxytocin and carbetocin.

2.2 SECONDARY OBJECTIVES

1. To correlate the effectiveness of the medication with clinical parameters
2. To document safety and evaluate adverse events recorded during the study.

3. STUDY DESIGN

Multiarm randomized controlled trial.

Random sequence will be generated using MS Excel by second supervisor.

Simple randomization 1:1:1 allocation ratio.
Allocation concealment will be achieved using central allocation (including telephone).
Participants, caregivers and outcome assessors will be blinded till the end of trial.

3.1 POPULATION

The population of this study comprises pregnant women beyond 37 weeks gestation undergoing elective caesarean section under regional anesthesia. 90 women will be selected according to inclusion and exclusion criteria.

3.2. STUDY TREATMENT AND DOSAGES

Misoprostol (200mcg Tablet) [Misotac, Sigma Pharmaceutical Industries, SAE, Egypt] Two tablets (400 mcg) in the buccal space just after delivery of the neonate during CS.

3.2.1. Supplies and Accountability

The treatment will be provided by main investigator (not indulged in patient selection or admission into the study) and stored in independent premises far from usual medicine held by authorized people. The study medications will be handed to be administered to the patient under supervision. The other investigators, indulged in management of the patient, will have to acknowledge receipt of all received treatments for the study.

3.3. STUDY ENTRY AND DURATION

3.3.1. RECRUITMENT AND RANDOMIZATION

During the pre-selection phase (whether in the antenatal clinic or after admission into hospital), exclusion and inclusion criteria will be applied. Suitable women will be invited to participate in the study then a signed and informed consent will be obtained from them.

When the patient's consent is obtained, they are to be included into the study.

3.3.2. Sample Size Justification

Results from previous study indicates that the need for additional oxytocic therapy in carbetocin therapy in comparison with oxytcin was reported to be 33.5% to 45.5% ***(Attilakos et al., 2010)****, while in sublingual misoprostol therapy in comparison with oxytocin was reported to be 26% and 43%* ***(Hamm et al., 2005).*** Using PASS 11, a sample size of 241 participants will be required to achieve 80% power and to detect an effect size (W) of 0.2 using 2-degree of freedom chi-square test with a significance level (alpha) of 0.05. An attrition rate of 5% is assumed. Therefore, 255 participants will be recruited in this multi-arm RCT. We decided to recruit 90 women in this arm to allow for participant withdrawal, break or loss of a package, etc. For this master degree thesis that is based on this multiarm trial, the candidate will collect the data of the arm of misoprostol (90 participants)

3.3.3. Study Duration

The duration of the study is 6 month.

3.4. Selection of Patients

3.4.1. Subjects' recruitment:

The population of this study comprises pregnant women at term (beyond 37 weeks gestation) with singleton pregnancies booked for elective caesarean section through a lower-segment transverse incision under spinal anaesthesia. Those patients within our trust will be approached to participate in this study. The patients will be approached around the 36th week. Patients will be given a handout explaining the study. Consent will be taken by the doctor involved with the patient. All participating personnel will be trained in explaining the study and obtaining informed consent.

3.4.2. Inclusion Criteria:

1. Age 18 years or more.
2. Gestational age of pregnancy of 37 completed weeks or more.
3. Written and signed informed consent by the patient to participate in the study.

3.4.3. Exclusion Criteria

1. fetal or maternal distress where, due to time constraints, it will not possible and/or appropriate to recruit or randomize.
2. Women undergoing caesarean section with general anesthesia are also excluded, because carbetocin is licensed for use with regional anaesthesia only.

3. Women planned to have any other type of uterine incision other than transverse lower segment.
4. Women with pre-eclampsia, eclampsia, and epilepsy.
5. Women with placental abruption are excluded because there is a higher risk of haemorrhage with these conditions and it was therefore felt to be inappropriate to recruit these women.
6. Women with thrombocytopenia, known coagulopathies, or receiving anticoagulant therapy.
7. Women with history of significant heart disease, hypertention requiring treatment, a history or evidence of liver, renal, vascular disease or endocrine disease (other than gestational diabetes).
8. Women with history of hypersensitivity to oxytocin or carbetocin.
9. Women with any severe allergic condition or severe asthma.
10. Women with any contraindication to receiving prostaglandins, including known hypersensitivity to misoprostol or other prostaglandins (PGs) or glaucoma.
11. Mental condition rendering the patients unable to understand the nature, scope and possible consequences of the study.