# *Sublingual Misoprostol to Reduce Blood loss during elective cesarean delivery: A randomised controlled trial*

Thesis

Submitted as Partial Fulfillment of Master Degree **in**

**Obstetrics and Gynecology**

By


## Mohamed Fathy Kamel

M.B.B.Ch -Ain Shams University -2008

Resident of Obstetrics &Gynecology

Berket Elsabaa General Hospital


**Under supervision of**


## *Prof. Karam Mohamed Bayoumy*

Professor of Obstetrics &Gynecology

Faculty of medicine –Ain Shams University

## *Dr. Amr Helmy Yehia*

Lecturer in Obstetrics &Gynecology

Faculty of Medicine-Ain Shams University

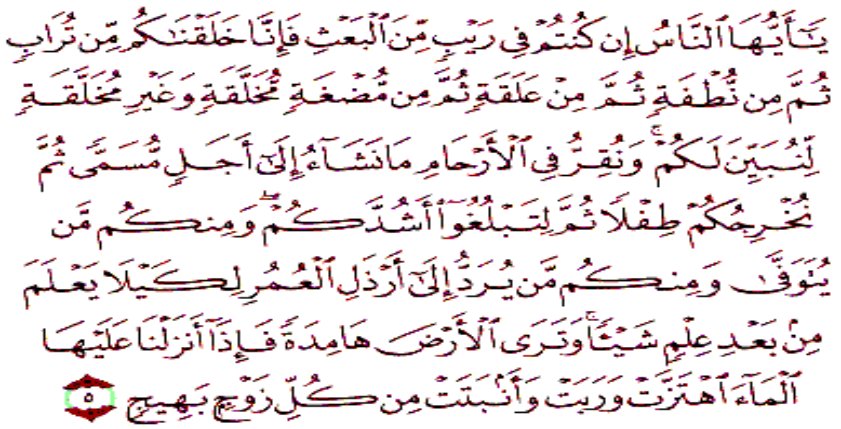


Faculty of Medicine

Ain Shams University

2017

# بسْمِ اللّهِ الرّحْمَنِ الرّحِيمِ


يَـٰٓأَيُّهَا ٱلنَّاسُ إِن كُنتُمْ فِى رَيْبٍ مِّنَ ٱلْبَعْثِ فَإِنَّا خَلَقْنَـٰكُم مِّن تُرَابٍ
ثُمَّ مِن نُّطْفَةٍ ثُمَّ مِنْ عَلَقَةٍ ثُمَّ مِن مُّضْغَةٍ مُّخَلَّقَةٍ وَغَيْرِ مُخَلَّقَةٍ
لِّنُبَيِّنَ لَكُمْ ۚ وَنُقِرُّ فِى ٱلْأَرْحَامِ مَا نَشَآءُ إِلَىٰٓ أَجَلٍ مُّسَمًّى ثُمَّ
نُخْرِجُكُمْ طِفْلًا ثُمَّ لِتَبْلُغُوٓا۟ أَشُدَّكُمْ ۖ وَمِنكُم مَّن
يُتَوَفَّىٰ وَمِنكُم مَّن يُرَدُّ إِلَىٰٓ أَرْذَلِ ٱلْعُمُرِ لِكَيْلَا يَعْلَمَ
مِنۢ بَعْدِ عِلْمٍ شَيْـًٔا ۚ وَتَرَى ٱلْأَرْضَ هَامِدَةً فَإِذَآ أَنزَلْنَا عَلَيْهَا
ٱلْمَآءَ ٱهْتَزَّتْ وَرَبَتْ وَأَنۢبَتَتْ مِن كُلِّ زَوْجٍۭ بَهِيجٍ ﴿٥﴾

صَدَقَ ٱللَّهُ ٱلعَظِيمْ

**سورة الحج: آية (٥)**

# Acknowledgements

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

*I would like to express my sincere gratitude to* ***Prof. Karam Mohamed Bayoumy,*** *professor of Obstetrics and Gynecology, Faculty of Medicine - Ain Shams University, under his supervision, I had the honor to complete this work, I am deeply grateful to him for his professional advice, his guidance and support.*

*I wish also to express my gratitude to* ***Dr. Amr Helmy Yehia,*** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for his great efforts, kind advice, support and encouragement throughout the whole work.*

*To my parents, my wife, my friends, my colleagues, my patients and to everyone who participated in one way or another in this work, I owe my thanks and appreciation.*

***Mohamed Fathy Kamel***

# Contents

# List of Abbreviations

| | |
|---|---|
| AARI | Average Annual Rate of Increase |
| CS | Cesarean Section |
| aPTT | Activated partial thromboplastin time. |
| BMI | Body Mass Index. |
| CBC | Complete Blood Count. |
| DIC | Disseminated Intravascular Coagulopathy. |
| HELLP | Haemolysis, Elevated liver enzyme levels, and Lowplatelets level. |
| MRI | Magnetic Resonance Imaging. |
| NSAIDS | Non Steroidal Anti-inflammatory Drugs. |
| PPH | Post Partum Hemorrhage. |
| PT | Prothrombin Time. |
| ABL | Allowable Blood loss |
| ABV | Average Blood Volume (Adult Women = 70ml/kg). |
| EBV | Estimated Blood Volume |
| Hi | Initial Hematocrit |
| Hf | Final Hematocrit |
| UI | Urinary incontinence |
| CI | Confidence Interval |
| ml | milli liter |
| mcg | mico gram |
| INR | International Normalization Ratio |
| LFT | Liver Function Test |
| CT | Computerized Tomography |
| WHO | World Health Organization |

# List of Abbreviations

| | |
|---|---|
| ACOG | American College of Obstetrics and Gynecology |
| PG | Prostaglandins |
| GLA | Gamma Lenolenic Acid. |
| A.A | Arachidonic Acid. |
| EAA | Eicosapentanoic Acid. |
| PKA | Protein Kinase A. |
| SD | Standard Deviation. |
| MLCK | Myosin Light Chain Kinase. |
| RCT | Randomized Controlled Trial. |
| MLCP | Myosin Light Chain Phosphate. |

# List of tables

# List of Figures

# *Sublingual Misoprostol to Reduce Blood loss during elective cesarean delivery: A randomised controlled trial*

Thesis

Submitted as Partial Fulfillment of Master Degree **in**

**Obstetrics and Gynecology**

By

**Mohamed Fathy Kamel**

M.B.B.Ch -Ain Shams University -2008

Resident of Obstetrics &Gynecology

Berket Elsabaa General Hospital

Under supervision of

***Prof. Karam Mohamed Bayoumy***

Professor of Obstetrics &Gynecology

Faculty of medicine –Ain Shams university

***Dr. Amr Helmy Yehia***

Lecturer in Obstetrics &Gynecology

Faculty of Medicine-Ain Shams University

Faculty of Medicine

Ain Shams University

2016

# Introduction

Cesarean section is one of the most commonly performed obstetrical operations all over the world. Epidemiologic data report a C.S. incidence of 20% - 30% worldwide, with comparable rates in high income and low income countries **(khawaja et al., 2009).**

Nonetheless, the trend toward an increasing reliance on C.S. has several disadvantages, including high rates of secondary infertility owing to postoperative adhesions **(Awonuga et al., 2011 )** . In addition, increased rates of abnormal placentation (including previa and accreta ), uterine rupture , blood transfusion and hysterectomy in future pregnancy have been reported **( Marshall et al., 2011 ) .**

Postpartum hemorrhage (PPH) is defined as blood loss of more than 500 ml following vaginal delivery or more than 1000 ml following cesarean delivery, a loss of these amounts within 24 hours of delivery is termed early or primary PPH, whereas such losses are termed late or secondary PPH if they occur 24 hours after delivery **(Sentilhes et al.,2016).**

Postpartum hemorrhage (PPH) is a leading cause of maternal mortality and morbidity, especially in low- resource countries. It is responsible for around 30% of maternal deaths world wide and 12% of survivors will have severe anemia **( Say et al.,2014).**

Uterine atony is a failure of the uterine myometrial fibers to contract and retract. This is the most important cause of PPH and usually occurs immediately following delivery of the baby, up to 4 hours after the delivery. **(Smith and Brennan, 2010).**

In order to reduce maternal mortality and morbidity its important to reduce the amount of bleeding during and after C.S. Medications, such as oxytocin, misoprostol, prostaglandin F2α and tranexamic acid have been used to control bleeding during and after C.S. **(Gungorduk et al.,2010).**

Oxytocin is routinely used to prevent uterine atony and excessive uterine bleeding during C.S. However, despite its effectiveness, 10-40% of women need additional uterotonic therapy. Secondary uterotonic agents such as methyl ergometrine or 15-methyl prostaglandin F2α are associated with adverse effects when administered within a dose range likely to be effective **(Kumar and Singh, 2012)**.

Misoprostol is a prostaglandin E1 analogue with potent uterotonic action and few adverse effects at therapeutic dose. It is readily absorbed when given by oral, sublingual, buccal, vaginal or rectal route. Its easy availability, relatively low cost, thermo stability, long shelf life and ease of administration all of which appear to make it particularly suitable for use in low resource setting in developing countries **(Al-Sawaf et al., 2013).**

Apharmacokinetic study compared the absorption kinetics of oral, vaginal, sublingual routes of administration of misoprostol found that sublingual misoprostol has the shortest time to peak concentration ,the highest peak concentration and the greatest bioavailability when compared to other routes. The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration, it takes 75 minutes. Therefore, it appears that sublingual and oral routes have the quickest onset of action. After 400µg of misoprostol, a sublingual dose achieves higher peak concentration than that of oral and vaginal administration. This is

due to rapid absorption through the sublingual mucosa as well as the avoidance of the first- pass metabolism via the liver. **(Tang et al., 2007).**

No clinically significant adverse hematological, endocrine, biochemical, immunological, respiratory, ophthalmic, platelets or cardiovascular effects have been found with misoprostol , shivering, nausea ,vomiting, fever >37.5°C within 24 h of delivery, headache and diarrhea are the major adverse reaction that have been reported consistently with misoprostol , but it is usually mild and self-limiting and will resolve in 2 to 4h**. (Tuncalp et al., 2012)**.

# Aim of the study

This study aims to evaluate the efficacy and safety of sublingual misoprostol in reducing blood loss during cesarean section.

## Study hypothesis

In women undergoing cesarean section, sublingual misoprostol may reduce blood loss.

## Study question

In women undergoing cesarean section, does sublingual misoprostol reduce blood loss?

# Patients and Methods

## Study design

Randomized, double blinded, prospective controlled trial.This clinical trial will be conducted at Ain-Shams University Maternity Hospital.

## Population of the study

A total of 158 women that will fulfill the inclusion criteria will be enrolled in the study, half of them will receive sublingual 400µg misoprostol (**Sigma)**, and the others will receive placebo.

## Sample Size Calculation

Sample size was calculated using PASS 11.0 sample size calculation program, and according to a study carried out by **Kumar and Singh, 2012.** 79 women were required in each arm to show a reduction in additional uterotonic therapy from 42.8 to 22.2 % with misoprostol (Power = 0.80,$\alpha$ = 0.05 and $\beta$ = 0.2). Based on estimated blood loss in women during cesarean section, taking mean blood loss, 65 women were required in each arm to show a reduction of blood loss from 651 ml with a SD of 118 ml to 595 ml with a SD of 108 ml with misoprostol (Power = 0.80, $\alpha$ = 0.05 and $\beta$ = 0.2).