



***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

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

يَا أَيُّهَا النَّاسُ إِن كُنْتُمْ فِي رَيْبٍ مِّنَ الْبَعْثِ فَإِنَّا خَلَقْنَاكُمْ مِّن تُّرَابٍ
ثُمَّ مِّن نُّطْفَةٍ ثُمَّ مِّن عَلَقَةٍ ثُمَّ مِّن مُّضْغَةٍ مُّخَلَّقَةٍ وَغَيْرِ مُخَلَّقَةٍ
لِّنُبَيِّنَ لَكُمْ وَنُقِرُّ فِي الْأَرْحَامِ مَا نَشَاءُ إِلَىٰ أَجَلٍ مُّسَمًّى ثُمَّ
نُخْرِجُكُمْ طِفْلًا ثُمَّ لِيَبْلُغُوا أَشَدَّكُمْ وَمِنْكُمْ مَّن
يُنْفِقُ وَمِنْكُمْ مَّن يَرُدُّ إِلَىٰ أَرْدَلِ الْعُمُرِ لِكَيْلَا يَعْلَمَ
مِن بَعْدِ عِلْمٍ شَيْئًا وَتَرَىٰ الْأَرْضَ هَامِدَةً فَإِذَا أَنزَلْنَا عَلَيْهَا
الْمَاءَ أَهْتَزَّتْ وَرَبَتْ وَأَنْبَتَتْ مِن كُلِّ زَوْجٍ بَهِيجٍ ﴿٥﴾

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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.

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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 F2 α 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 F2 α 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 400 μ g 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 $>37.5^{\circ}\text{C}$ within 24 h of delivery, headache and diarrhea are the major adverse reactions 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 $\beta = 0.2$).