SUBLINGUAL MISOPROSTOL VERSUS OXYTOCIN INFUSION TO REDUCE BLOOD LOSS AT CESAREAN SECTION

A thesis submitted for the partial fulfillment of master degree in Obstetric and Gynecology

By

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Abstract

The aim of the study: Is to compare the effect of Sublingual misoprostol and intravenous oxytocin in controlling blood loss during and following cesarean section.

Method: This is a prospective study where one hundred and three pregnant women undergoing cesarean section were recruited from emergency unit of obstetric department, Kasr El Aini hospital. Women were randomly assigned to receive sublingual misoprostol or I.V oxytocin following delivery of baby. The amount of blood loss as well pre and post- operative Hb were calculated. Side effects in both groups were also recorded.

Results: The study included 103 pregnant women with singleton term undergoing C.S under regional anesthesia. Group, A (n=50) received 400µg sublingual misoprostol and group B (n=53) received 20U I.V oxytocin on 500ml lactated ringer solution. No statistically significant difference was found between the two groups regarding the mean blood loss, hemoglobin decrease and percent of hemoglobin decrease (P value >0.999). Side effects were reported in the misoprostol group (9.3% shivering and 18.6% vomiting) while no side effects were recorded in the oxytocin group (P value 0.001).

Conclusion: According to the present study sublingual misoprostol (400 µg) is as effective as IV infusion of oxytocin (20 U) regarding mean blood loss during cesarean section, however side effects of misoprostol are higher.

Keywords:
(Misoprostol, Oxytocin, Postpartum hemorrhage)
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List of Abbreviation

PPH Post partum hemorrhage
OTR Oxytocin receptor
Mu/MIN Milliunit /minute
IU International unit
I.M Intramuscular
I.V Intravenous
PGSE1 Prostaglandin E1
T max Total maximum
TOP Termination of pregnancy
C.S Cesarean Section
U Unit
NS Normal saline
FFP Fresh frozen plasma
DIC Disseminated intravascular Coagulopathy
RBCS Red blood cells
±SD Standard deviation
Hrly hourly
WHO World Health Organization
Hb Hemoglobin
INTRODUCTION

Post partum hemorrhage (PPH) continues to be a leading cause of maternal morbidity and mortality worldwide. According to the World Health Organization estimates, more than 585,000 women die every year from pregnancy-related cause, of which 25% were due to severe bleeding (WHO 1998).

According to the World Health Organization obstetrics hemorrhage causes 127,000 deaths annually world wide and is the leading cause of maternal mortality (WHO, 2008).

The rate of cesarean delivery is increasing, the percentage is estimated to be around 20% in Egypt (Khawaja 2004) and the average blood loss during cesarean delivery (1000ml) is almost double the amount lost during vaginal delivery (500ml) (Magann 2005). Primary postpartum hemorrhage is the loss of more than 500ml of blood within the first twenty-four hours of delivery or loss of any amount that is enough to cause hemodynamic instability in the mother or loss of more than 10% of the total blood volume. It is the most common form of post partum hemorrhage (WHO 2008-Khan 2006).

Uterine atony is the commonest cause of primary PPH and complicates 1 in 20 deliveries. Risk factors for uterine atony include uterine over distention (multiple gestation polyhydramnios, fetal macrosomia), prolonged oxytocin use, abnormal labor, grand multiparity, chorioamnionitis, placenta previa, and use of uterine-relaxing agents (tocolytic therapy, halogenated anesthetics,

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nitroglycerin (Didly, 2002). However these preparations are associated with adverse effects which may cause many complications. Reduction of operative blood loss at cesarean section is beneficial to the patient in term of decreased post operative morbidity and decrease in risk associated with blood transfusion. (Prendiville2001).

Active management of third stage of labor by administration of uterotonic drugs reduce the risk of postpartum hemorrhage, post partum anemia as well as the need for blood transfusion.

Therefore, active management should be the routine management of choice (prendiville et al 2000).

The most commonly used utrotonic drugs include oxytocin, methergin and prostaglandins. They are very effective in reducing the mean blood loss and post partum hemorrhage (Elbourne et al., 2001). Oxytocin is usually given by intravenous infusion of 10-20IU in 500 ml Rings lactate, the main advantages of which are its rapid onset of action and that it does not raise the blood pressure (Davies, 2005). Intravenous oxytocin has very short half life (10-40mint), therefore the potential advantage of an oxytocin infusion of cesarean section is maintain once of uterine contractility throught the procedure. (lukugamage AU, 2001) Although oxytocin is considered to be a safe drug it can cause tachycardia and hypotension, it has anti diuretic, negative inotropic and antiplatelet effects. (Thomas JS, KOSH, 2007) Misoprostol is a synthetic prostaglandin E1 analogue, it is wildly used in obstetrics and gynecology for cervical ripening, termination of pregnancy, induction of labour, management of the third stage of labour and for
intractable postpartum hemorrhage as a last resort when other medical interventions are not sufficient. (Gulmezoglu et al, 2007). Misoprostol, a prostaglandin E1, analogue has a potent uterotonic effect, cheap, stable at room temperature, easily administered and has few adverse effects. It is well absorbed when administered by oral, vaginal, rectal, sublingual or buccal routes. Misoprostol administration either by oral or rectal route has been shown to be effective in prevention of PPH and is considered as an effective alternative to oxytocin especially in developing countries. (Prata et al., 2006 and Steven et al., 2007)

Recent pharmacokinetic studies suggest that the bio-availability of misoprostol after sublingual administration is higher than oral or vaginal administration) (Tang 2002).

Side effects of misoprostol include shivering, pyrexia, nausea, vomiting and diarrhea (lumbigonan et al 2002).
AIM OF WORK

The aim of this study is to compare the effectiveness of sublingual misoprostal administered immediately after delivery of the neonate at cesarean section versus intravenous oxytocin infusion in the prevention of uterine atony and thereby reducing blood loss. The amount of blood loss is estimated by comparing pre and postnatal maternal hemoglobin level.
OXYTOCIN

1- Pharmacology of oxytocin
   a. Structure and chemistry of oxytocin
   b. Synthesis and processing of oxytocin
   c. Control of oxytocin
   d. Pharmacodynamic of oxytocin
   e. Pharmacokinetics of oxytocin

2 – Clinical uses of oxytocin
   a. Induction and augmentation of Labor
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   c. Prevention of postpartum hemorrhage
   d. Treatment of atonics post partum hemorrhage

3 – Disadvantage of oxytocin

Fig. (I): Structure of oxytocin
2- Pharmacology of oxytocin

A-Structure and chemistry of oxytocin

Oxytocin is a peptide of nine amino acids its amino acid sequence is: cysteine – tyrosine – isoleucine–glutamine-asparagine–cysteine – proline – glycine. The structure of oxytocin is very similar to that of arginine vasopressin, whose sequence differs from oxytocin 2 amino acids. (Guyton, 2006)

B-Synthesis and processing of oxytocin

Oxytocin and arginine vasopressin (AVP) are synthesized in the endoplasmic reticulum of monocular neurons located in the supraoptic and paraventricular nuclei of the hypothalamic as pre-prohormones. In the Golgi apparatus, they are packaged in secretory granules and are transported down the hypothalamus – hypophysial tract. During transport, the precursor hormones are processed, yielding the final hormone and the respective neurophusins the contents of the neuro secretory vesicles are released by exocytose from the axon terminals in the posterior pituitary.

Exocytosis triggered by the influx of Ca\(^{2+}\) through voltage-gated channels that are opened during neuronal depolarization. These neuropeptides enter the systemic circulation through venous drainage of the posterior pituitary into the intercavernous sinus and internal jugular vein. (Molina, 2006).
c - Control of Oxytocin release

The principal stimulus for oxytocin release is mechanical stimulation at the end of gestation. Oxytocin release is also stimulated by the forceful contractions of the uterus acts through positive feedback mechanisms during parturition to stimulate oxytocin neurons and this further increases the secretion of oxytocin. Oxytocin release is also triggered by stimulation of tactile receptors in the nipples of the lactating breast during suckling. Breast – feeding generates sensory impulses that are transmitted to the spinal cord and then to the oxytocin producing neurons in the hypothalamus the information transmitted by these sensory afferents produces intermittent synchronized burst firing of oxytocin neurons, resulting in pulsatile release of oxytocin and increases in blood oxytocin concentration.

In addition to its secretion from neuro-hypophysial terminals of the posterior pituitary, oxytocin is released within the hypothalamic supraoptic and paraventricular nuclei the function of this intra-hypothalamic release of oxytocin is to control the activity of oxytocin neurons in an autocrine fashion by a positive feedback mechanism, increasing the neurohypophysial release of oxytocin. The release of oxytocin is inhibited by sever pain, increased body temperature, and loud noise. The role of oxytocin in males is not clear, although recent studies have suggested that it may participate in ejaculation. (Molina, 2006)
**Pharmacodynamics of oxytocin**

The best known mechanism for oxytocin effect on myometrial contractility is by increasing the intracellular concentration of calcium this is achieved by the release of calcium deposited in the endoplasmic reticulum and by enhanced entry of extracellular calcium.

Oxytocin receptors are present in tissues other than the uterus, such as liver, pancreas, mammary gland, and endometrium. The myometrial oxytocin receptor (OTR) concentration is the rate limiting step for oxytocin action. The OTR is not present in non-pregnant myometrium. It appears in myometrial cells at approximately 13 weeks of gestation and increase concentration until term, when there is a five-fold increase in OTR density as compared with the non-pregnant uterus. There is no increase in the number of OTRs during labor, the distribution of OTRs in the pregnant human uterus shows a steep downward gradient, with concentrations in the lower uterine segment, isthmus and cervix being remarkably less than in the fundus of the uterus. The concentration of OTRs is hormonally regulated, treatment with estradiol increases myometrial OTR concentration whereas progesterone has the opposite effect (Arias, 2000).

Oxytocin may stimulate uterine contraction by mechanisms independent of intracellular calcium concentration, it has been found that plasma concentrations of prostaglandin E (PGE) and prostaglandin F (PGF) increase during oxytocin administration (Arias, 2000).
Pharmacokinetics of oxytocin

The plasma concentration of oxytocin is similar during pregnancy and during the latent and active phases of labor, however there is a significant increase in the plasma level of oxytocin during the last part of the second stage of labor, the highest concentration of oxytocin during labor is found in umbilical cord blood, indicating that there is a significant production of oxytocin by the fetus during labor (Arias F, 2000).

Endogenous oxytocin is secreted in pulsatile form during spontaneous labor, a fact that is reflected in the marked variability observed in minute – to minute measurements of maternal plasma oxytocin concentration, this has resulted in significantly less oxytocin being used to achieve vaginal delivery as compared with the infusion method. Oxytocin can be administered by any parenteral route. It also is absorbed by the buccal and nasal mucosa. When administered orally, oxytocin is rapidly inactivated by trypsin. The intravenous route is used almost exclusively to stimulate the pregnant uterus because it allows precise measurement of the amount of medication being administered and a relatively rapid discontinuation of the drug when side effects occur. (Arias F, 2000).

Once absorbed, oxytocin is distributed in the extracellular fluid and does not bind to proteins. Between 20 and 30 minutes are required for oxytocin to reach a steady–state plasma level, therefore, it is unnecessary and potentially harmful to adopt intervals of less than 30 minutes to increase the amount of the medication during induction or augmentation of labor. Shorter intervals may decrease the length of
the induction of labor but they are more likely to be associated with uterine hyper stimulation and fetal distress. A continuous intravenous infusion of oxytocin cause a linear increase in plasma oxytocin concentration that reaches a maximum in approximately 40 minutes, the time necessary to achieve uterine response is dose dependent and varies from 14 to 60 minutes when the dosage used is between 1 and 16mU/min. approximately 45% of patients require less than 2.5mU/min, 45% require from 2.5 to 5.0mU/min and 10% will need more than 5mU/min. The half-life of oxytocin is 10 to 12 minutes. The metabolic clearance rate is similar for men, pregnant and non pregnant women which is 20 to 27 ml/kg per minute. The similarity of the metabolic clearance rate between men and pregnant females is striking in view of the large increase that occurs during pregnancy in the plasma concentration of leonine –amino peptidase, an enzyme capable of hydrolyzing oxytocin. This suggestes that factors other than this enzyme are responsible of the degradation of oxytocin (Arias, 2000).

III. Clinical uses of oxytocin

Syntocinon® (synthetic oxytocin) is available in ampoules containing 5IU in 1 mL and 10 IU in 1 mL.

A. Induction and Augmentation of Labour

Induction implies stimulation of contractions before the spontaneous onset of labour, with or without ruptured membranes.

Augmentation refers to stimulation of spontaneous contractions that are considered inadequate because of failure of progressive
cervical dilatation and fetal descent. The goal of induction or augmentation is to effect uterine activity sufficiently to produce cervical change and fetal descent. Oxytocin is the drug of choice for labour induction. It is administered by intravenous infusion of a diluted solution (typically 10mIU/mL), preferably by means of an infusion pump. Some physicians use a Low-dose protocol involving an initial dose of 1 mIU/minute every 30 to 40 minute, this is avoid non reassuring fetal status.

Other authorities advocate a High-dose protocol, with starting doses of 6 mIU/minute and increases of up to 2 mIU/minute at 20-minute intervals some published trials have suggested that the high-dose regimens resulted in a shorter mean admission-to-delivery time, fewer failed induction, fewer forceps deliveries, fewer cesarean deliveries for dystocia and decreased intrapartum chorioamnionitis or neonatal sepsis (Cunningham et al, 2005).

**B. Oxytocin challenge test**

In patients whose pregnancy holds increased risk for maternal or fetal complications (e.g. maternal diabetes mellitus or hypertension), an oxytocin challenge test can be used to assess fetal well-being. Oxytocin is infused intravenously, initially at a rate of 0.5mIU/minute, this rate is increased slowly until 3 uterine contractions occur in 10 minutes concurrent monitoring of the fetal heart rate indicates whether or not the uterine contractions are associated with changes in fetal heart rate known to be associated with fetal distress, the outcome of the oxytocin challenge test is helpful in determining the presence of adequate placental, reserve for
continuation of high-risk pregnancies (Good man and Gilman’s 2006).

C. Prevention of postpartum haemorrhage

The primary purpose of active management of the third stage of labour is to reduce the risk of PPH. Active management includes administration of a prophylactic uterotonic at or after delivery of the baby, early cord clamping and cutting, controlled cord traction to delivery the placenta, and uterine massage. Prophylactic use of oxytocin regardless of other aspects of active management of the third stage of labour, was evaluated in a Cochrane review entitled “Prophylactic oxytocin in the third stage of labour”. This review includes comparisons of:

1. Oxytocin versus placebo or no uterotonic,
2. Oxytocin versus ergot alkaloids (ergometrine) and
3. Oxytocin plus ergometrine (Syntomertine®) versus ergometrine alone in the management of the third stage of labour.

Oxytocin use was found to halve the risk of PPH with blood loss ≥ 500 ml and decreased the risk of severer PPH with blood loss ≥ 1000 ml; these findings were consistent regardless of whether oxytocin was used as part of the active management approach or on its own, or whether it was given after or before delivery of the placenta. A significant reduction in the use of additional uterotonics was also found. Addition of ergometrine to oxytocin increases the incidence of high blood pressure and vomiting (Cotter et al., 2001).