Introduction

Hysterectomy is the surgical removal of the uterus. It is the most frequently performed major gynaecological surgical procedure, with millions of procedures performed annually throughout the world **(DeLancey et al., 2013).**

Hysterectomy can be performed for benign and malignant indications. Approximately 90% of hysterectomies are performed for benign conditions, such as fibroids causing abnormal uterine bleeding; other indications include endometriosis/adenomyosis, dysmenorrhoea, dyspareunia and prolapsed **(Panda et al., 2015).**

Hemorrhage requiring blood transfusion is one of the most frequently cited complications of total abdominal hysterectomy, occurring in 2%–12% of cases **(Osler et al., 2011).**

Various methods had been adopted by researchers to lessen blood loss during TAH. Preoperative administration of gonadotropin-releasing hormone (GnRH) analogs have been found to be effective in reducing the size and vascularity of large myomas; however, significant adverse effects like hot flushes and osteoporosis have been reported after its use **(Lethaby et al., 2002)**.

Although injection of vasopressin in the lower uterine segment was found to be beneficial in reducing blood loss during abdominal hysterectomy, serious complications such as hypotension, myocardial infarction, and cuff cellulitis have been reported after use of this drug **(Duhan et al., 2010).**

Misoprostol, a synthetic analogue of prostaglandin E1, has been extensively evaluated as an uterotonic agent in obstetrics mainly for prevention and management of postpartum hemorrhage and reduction of bleeding during cesarean delivery **(Ellis et al., 2010).**

The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. The peak concentration is achieved about 30 minutes after sublingual administration, a sublingual dose achieves a 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 **(Laura et al., 2016).**

Among non-pregnant women, misoprostol has been used for cervical priming before trans-cervical procedures **(Fiala et al., 2007)**, and for reducing blood loss in myomectomy **(Kongnyuy et al., 2008)** and laparoscopy-

assisted vaginal `hysterectomy with promising results **(Chang et al., 2006).**

Misoprostol can cause direct vasoconstriction in uterine arteries and this property of misoprostol is most likely to be beneficial in reducing blood loss during TAH **(Okin et al., 2001).**

Strong myometrial contractions induced by misoprostol indirectly cause relative avascularity in the myoma and may also contribute to a reduction in bleeding. In addition, a decrease in uterine artery blood flow in myoma has been observed by Doppler velocimetry after misoprostol administration **(Celik et al., 2003)**.

Aim of the Work

The aim of the present study is to investigate whether preoperative administration of sublingual misoprostol is beneficial in reducing intraoperative blood loss among women undergoing total abdominal hysterectomy.

Research hypothesis:

- In women undergoing total abdominal hysterectomy, Preoperative administration of sublingual misoprostol could be beneficial in reducing intraoperative blood loss.

Research question:

- In women undergoing total abdominal hysterectomy, does preoperative administration of sublingual misoprostol beneficial in reducing intraoperative blood loss?

Chapter (1)

Misoprostol

Prostaglandins (PG) are molecules responsible for physiologic reactions that act as intermediaries in several processes involved during pregnancy including term, labour, postpartum involution, and placental-fetal vascular dynamics. Their biosynthesis is limited by the activity of the enzyme arachidonic acid cyclo-oxygenase, which catalyses the transformation of arachidonic acid into prostaglandin **(Bakker et al., 2017).**

Prostaglandins receptors are present in both, pregnant and nonpregnant, uteri and their concentration in the myometrial tissue increases at the beginning of labour. Prostaglandins have effects on the myometrium and cervix, whereas the activity of oxytocin is limited to the uterine muscle and it is in fact, strictly dependent on calcium concentration **(Ozge et al., 2012).**

Prostaglandins E and F are the most important types of prostaglandins with uterotonic activity and have a relevant advantage compared with oxytocin in terms of biological activity. Prostaglandins E and F can be administered, and are absorbed by any route including intravenous, oral, sublingual, vaginal or intracervical

administration with variable incidence of side-effects **(Grillo-Ardila et al., 2014).**

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analogue was developed for gastric ulcer prevention but commonly used in reproductive health because of its uterotonic and cervical priming action **(Laura et al., 2016).**

In comparison to other prostaglandin analogues, misoprostol has the advantages of being cheap, widely available, stable at room temperature and having few side effects **(Allen and O'Brien, 2009).**

Misoprostol was originally developed as a tablet for oral administration, but extensive research has been conducted on misoprostol used by various other routes including buccal, sublingual, rectal and vaginal **(Tang et al., 2007).**

Structure and chemistry of misoprostol:

The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion in 1967 by Robert A and colleagues; However, naturally occurring prostaglandins have three drawbacks that hindered their clinical application:

These problems were: (1) rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally, (2) numerous side effects, and (3) chemical instability leading to a short half life **(Tang et al., 2007).**

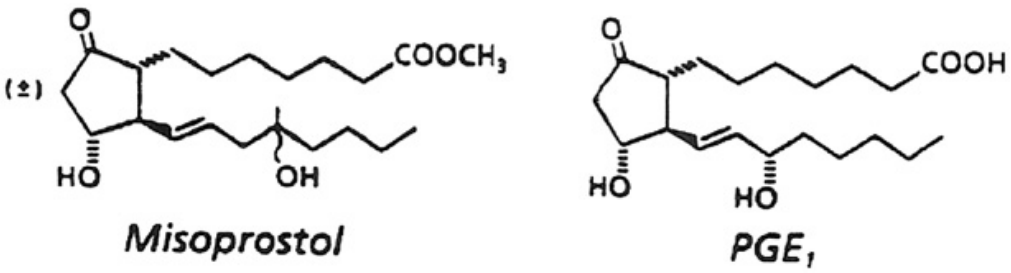

Fig. (1): The structures of misoprostol and the naturally occurring prostaglandin E1 **(Tang et al., 2007).**

Misoprostol differs structurally from prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15. The methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, whilst the movement of the hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety profile of the drug **(Ellis et al., 2010).**

Pharmacokinetic properties of the various routes of administration of misoprostol:

Misoprostol tablets were developed to be used orally. Other routes of administration, however, including vaginal, sublingual, buccal and rectal, have also been used extensively in obstetric and gynecological applications. **(Dodd et al., 2010).**

The time to peak concentration (Tmax) represents how rapidly the drug can be absorbed; the peak concentration (Cmax) reflects how well the drug is being absorbed while the area under the serum concentration versus time curve (AUC, equivalent to bioavailability) denotes the total exposure to the drug **(Khan and El-Refaey, 2004).**

1- Oral route:

After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid **(Laura et al., 2016).**

Following a single dose of 400 μg oral misoprostol, the plasma misoprostol level increases rapidly and peaks at about 30 minutes (Fig. 2) declines rapidly by 120 minutes and remains low thereafter **(Tang et al., 2007).**

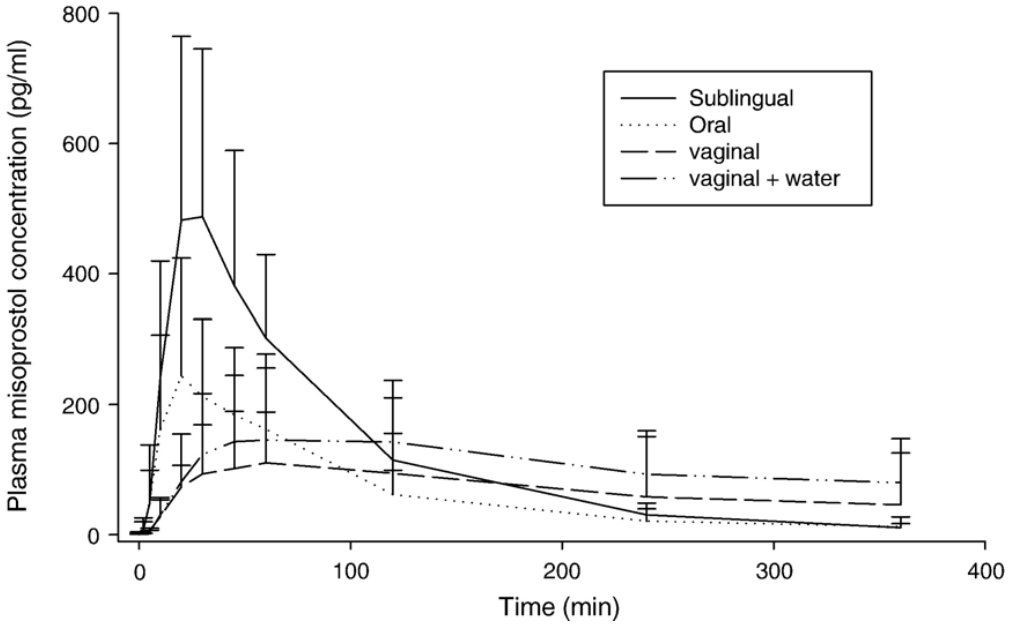

Fig. (2): Mean plasma concentrations of misoprostol acid over time (arrow bars=1 SD) **(Tang et al., 2007).**

2- Vaginal route:

In contrast to the oral route, the plasma concentration increases gradually after vaginal administration, reaching its maximum level after 70-80 minutes before slowly declining with detectable drug levels still present after 6 hours **(Ellis et al., 2010).**

In clinical practice, remnants of tablets are sometimes seen many hours after vaginal administration, indicating that the absorption is variable and incomplete. This may be due to the variation between women in the amount and pH of the vaginal discharge. Variation in the

amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal mucosa **(Hofmeyr et al., 2010).**

Numerous attempts have been made to improve the absorption of vaginal misoprostol. The addition of water to the misoprostol tablets is a common practice. However, this has been shown not to improve the bioavailability of vaginal misoprostol **(Castleman et al., 2006).**

3- Sublingual route:

The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue.

Sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes **(Tang et al., 2007).** (Fig. 2)

The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration, it takes 75 minutes **(Castleman et al., 2006).**

After 400 μg of misoprostol, a sublingual dose achieves a 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 **(Schaff et al., 2005).**

The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factors. The rapid onset and high peak concentration means that of all the possible routes the systemic bioavailability, as measured by the AUC in the first 6 hours, is greatest for sublingual administration **(Laura et al., 2016).**

4- Buccal route:

Buccal administration is another way of giving misoprostol. The drug is placed between the teeth and the cheek and allowed to be absorbed through the buccal mucosa. Clinical studies, although limited compared to other routes, have shown that the buccal route is also effective for medical abortion, cervical priming and labor induction **(Middleton et al., 2005).**

The shape of the buccal route absorption curve is very similar to that for vaginal absorption but the serum drug levels attained are lower throughout the 6 hours study period **(Tang et al., 2007).** (Fig. 3)

The buccal route is a promising way of administering misoprostol and more studies are required to compare it with other routes of administration. **(Laura et al., 2016).**

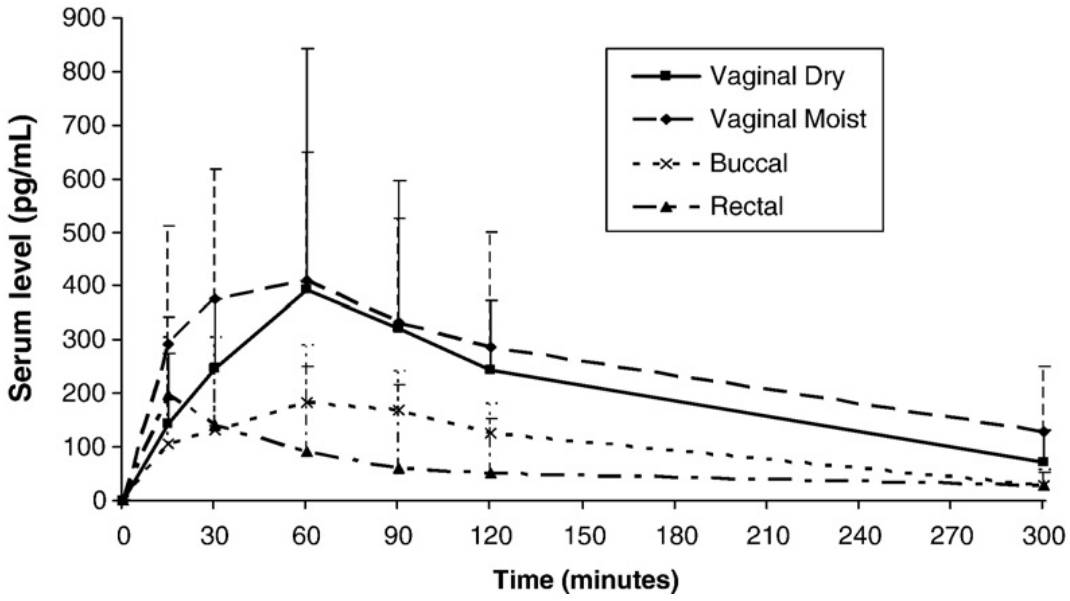

Fig. (3): Mean serum levels of misoprostol acid in pg/mL for four epithelial routes of misoprostol administration over 5 hours. Error bars represent standard deviation **(Tang et al., 2007).**

5- Rectal route:

The rectal route of administration has been studied for the management of postpartum hemorrhage. This route of administration is less commonly used for other applications **(Leon et al., 2012).**

The shape of the absorption curve after rectal administration is similar to that of vaginal administration but its AUC is only 1/3 that of vaginal administration period **(Tang et al., 2007).** (Fig. 3)

The mean Tmax after rectal administration is 40-65minutes.

6- Intracervical administration:

Intracervical misoprostol at a single dose of 50 µg appears to be an effective method for induction of labor at term, but caution should be taken with cases of unfavourable cervix **(Hofmeyr et al., 2010).**

An understanding of the pharmacokinetic properties of different routes of administration can help to design the best regimens for the various clinical applications. However, it may not be able to predict clinical outcomes for various clinical indications **(Laura et al., 2016).**

Sublingual misoprostol, which has the shortest Tmax, is perhaps useful for clinical applications that require a fast onset of clinical action, such as postpartum hemorrhage or cervical priming **(Winikoff et al., 2010).**

Vaginal misoprostol on the other hand, which has a high bioavailability and sustained serum level, is useful for indications that require a longer time for the manifestation

of its clinical effects, like medical abortion **(Raymond et al., 2013).**

The absorption kinetics can also explain why some routes of administration are associated with a higher incidence of side effects. Sublingual administration, which gives the highest Cmax, is associated with highest incidence of side effects when compared to other routes **(Khan and El-Refaey, 2003).**

Pharmacokinetics in human breast milk:

Misoprostol was detected in breast milk within 30 minutes of oral administration. The peak concentration was attained in 1 hour, which is slightly slower than the plasma level (30 minutes). The level in breast milk rapidly drops afterwards and is undetectable by 4-5 hours after ingestion. The misoprostol acid level in breast milk is only one-third of that in the plasma **(Vogel et al., 2004).**

However, breastfeeding women should be advised that misoprostol may cause infant diarrhea **(Hale, 2004).**

Effects on the uterus and the cervix:

First, misoprostol causes contractions of the smooth muscles lining the uterus that is instrumental in emptying the uterus of its contents. Second, it softens the cervix, allowing greater dilatation for intrauterine procedures as

well as facilitating expulsions from the uterus **(Bakker et al., 2017).**

Uses of Misoprostol:

A- Misoprostol in Obstetrics:

Misoprostol is potent and valuable drug for managing and treating a wide range of obstetric conditions including postpartum hemorrhage, intra-uterine fetal death, labor induction, first and second trimester abortion, incomplete and missed abortion **(Rebecca and O'brien, 2009).**

1) Medical Management of Miscarriage :

Misoprostol is an option for the medical management of early pregnancy failure, including anembryonic pregnancies and embryonic demise, and incomplete abortion for women at 12 weeks or less of gestation **(Chen et al., 2007).**

Contraindications include pelvic infection or sepsis, hemodynamic instability or shock, allergy to misoprostol, known bleeding disorder, concurrent anticoagulant therapy, and confirmed or suspected ectopic or molar pregnancy **(Neilson et al., 2006).**