Introduction

The American Congress of Obstetricians and Gynecologists (ACOG) defines postpartum hemorrhage (PPH) as the loss of more than 500 mL of blood after vaginal delivery and the loss of 1000 mL or more after CD ***(ACOG, 2006).***

PPH is considered the most preventable cause of maternal mortality, here becomes the importance of its prevention, and so all patients with risk factors for PPH should be identified and counseled, as appropriate for their level of risk. Planning for these patients involves ensuring availability of resources that might be needed, including personnel, medication, equipment, and blood products ***(Hofmeyr et al., 2008).***

In order to obtain that, all medical facilities should have protocols for dealing with PPH and obstetric hemorrhage ***(Smith & Brennan, 2010).***The management of bleeding in cesarean section is a shared responsibility between obstetricians and anesthetists. Major hemorrhage continues to be one of the most common causes of direct maternal death in deaths in obstetric practice ***(Esler et al., 2003).***

The active management of the third stage of labor has been shown to decrease the incidence and severity of postpartum hemorrhage ***(Hofmeyr et al., 2008).*** It decreases the risk of postpartum hemorrhage (PPH) by 60%**,** and up to 68%; it is much better than expectant management, in which the placenta is allowed to separate spontaneously aided only by gravity or nipple stimulation***(Anderson & Etches, 2007).***

Misoprostol, which is a prostaglandin E1 (PGE1) analogue, has potent uterotonic action, is cheap and stable at room temperature, and has few adverse effects. It is well absorbed when administered by oral, vaginal, sublingual, rectal, or buccal routes ***(Gulmezoglu et al., 2007).*** These properties have attracted great interest in the drug as an affordable method for preventing and treating postpartum hemorrhage in both low and middle income countries ***(WHO statement, 2009),*** and it also showed promising results in reducing blood loss after delivery ***(Gülmezoglu et al., 2007).***

Its use as a potent uterotonic agent has been extensively studied in the prevention and treatment of PPH after vaginal delivery (***Nasr et al., 2009***). Prevention and treatment of PPH have depended primarily on injectable uterotonics, which are seldom available for births outside the health system. For these reasons, the use of misoprostol to prevent or treat postpartum hemorrhage has attracted considerable attention. Misoprostol, an inexpensive and stable prostaglandin E1 analogue, has been shown to stimulate uterine contractility in early pregnancy and at term (***Norman et al., 1991).***

Previous studies have addressed protocols to limit excessive blood loss during elective CS. Most of these studies compared different doses and routes of administration of misoprostol to different concentrations and infusion rates of oxytocin, both drugs being given at roughly the same time and generally after cord clamping(***Munn et al., 2001); (Nasr et al., 2009).***Although it is likely that every maternity unit has a different practice for prophylaxis against excessive bleeding in

conjunction with CS, infusion of oxytocin remains the standard practice (***Munn et al., 2001).***Nevertheless, misoprostol has several advantages over oxytocin, particularly with respect to cost, ease of administration (via several routes), adverse effect profile, and potency. Also, when it is added sublingually to injectable oxytocin after cesarean section, it shows more effectiveness than oxytocin alone***(Fekih et al., 2009).***

Sublingual ***(Vimala et al., 2006)***, oral ***(Acharya et al., 2001)*** ***(Lapaire et al., 2006)*** and buccal (***Hamm et al., 2005)*** administration of misoprostol have all been used for PPH prophylaxis during cesarean section as well as treatment for established PPH after cesarean section***(Lokugamage et al., 2001).***

Rectal administration of misoprostol was found to be superior to oral administration for management of the third stage of labor, and rectally administered misoprostol has also been used with promising results for the prevention and control of PPH after vaginal births ***(Nasr et al., 2009)***. Rectal administration of misoprostol has been used for prevention of PPH after vaginal delivery with encouraging results ***(Karkanis et al., 2002);*** (***Parsons et al., 2007)***. Rectally administered misoprostol is associated with slower absorption, lower peak levels, and reduced adverse effects when compared with the oral and sublingual routes ***(Khan & El-Refaey, 2003)***; therefore, it was the preferred route of administration in the present study. Doses ranging from 200µg to 1000µg were previously used ***(Khan& El-Refaey, 2003***); ***(Tang & Ho, 2006).***

Aim of Work

The aim of work is to compare the efficacy of the rectal PGE1 synthetic analogue (misoprostol) 200, 400 and 600 microgram before cesarean section to decrease blood loss during and after the operation.

Chapter (1)

Misoprostol

Prostaglandins are lipid autacoids ***(Ricciotti& FitzGerald, 2011)***, which are produced naturally by the body ***(Quinn, 2007)***and act like hormones in that they act as chemical messengers, but do not move to other sites ***(Ophardt, 2003).***They are produced by all body cells except RBC's with profound physiological effects at very low concentrations ***(Sturm, 2010).***

Types of prostaglandins (3 main types):

- Type1 and 2: are produced by omega6-fatty acids.
- Type3: which is produced by omega3-fatty acids.

Each one of these types has its specific precursor as follows:

- Type 1 is derived from GLA (Gamma- lenolenic acid).
- Type 2 is derived from AA (Arachidonic acid).
- Type 3 is derived from EAA (Eicosapentanoic acid).

These prostaglandins are further more classified into types from A to H depending on the substituent on the cyclopentane ***(BCH, 2006).***

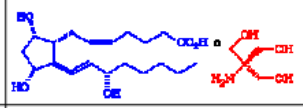
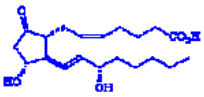
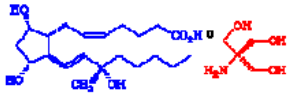
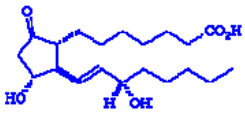
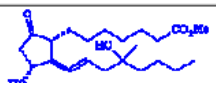
Name	Structure	Comments
Dinoprost Tromethamine PGF2a Prostin F2a		Use to induce abortion Salt given by intraamniotic administration
Dinoprostone PGE2 prostin E2		Use to induce abortion Administered as a vaginal suppository.
Carboprost Tromethamine PGF2a (S)-Methyl-PGF2a		Use to induce abortion or to ameliorate severe postpartum hemorrhage
Alprostadil PGE1 prostin VR Pediatric		For use in neonates with patent ductus until surgery can be performed to correct this congenital defect.
Misoprostol (R,S)-Methyl-16-Hydroxy-PGE1, Methyl ester		Gastric antisecretory and gastroprotective effects

Figure (1): Different types of Prostaglandins and their applications ***(BCH, 2006).***

Structure of Prostaglandins

Prostaglandins are unsaturated carboxylic acids, consisting of a 20-carbon skeleton that also contains a five-member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five-member ring there may also be double bonds, a ketone, or alcohol groups ***(Ophardt, 2003).***

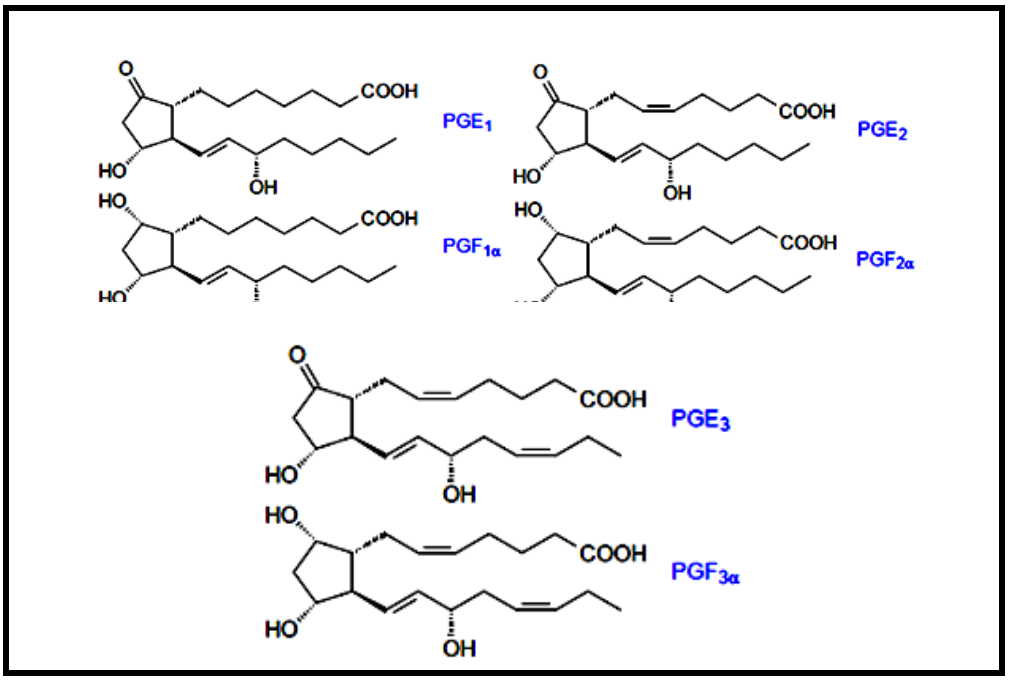


Figure (2): Structure of PGE, PGF ***(Christie, 2012).***

Prostaglandin E1 and F1 are formed fromLinolenic acid as shown in figure 3.

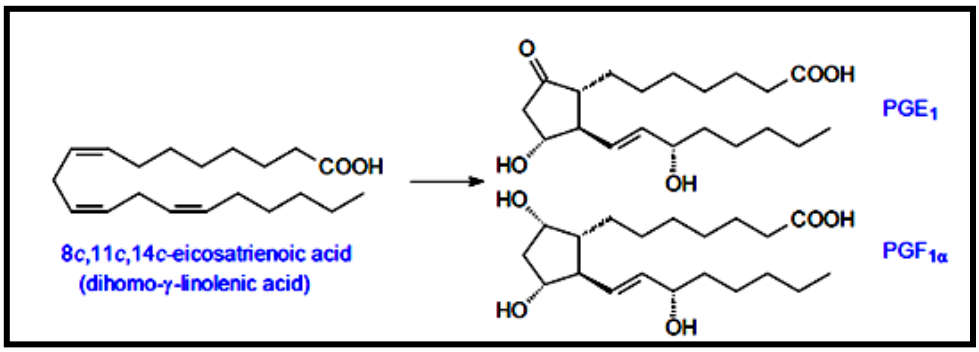


Figure (3): Biosynthesis of PGE1 and PGF1 from linoleic acid (***Christie, 2012).***

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 C-15. It appears that

the methyl ester at C-1 increases the antisecretory potency and duration of action of misoprostol, while the movement of hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improve oral activity, increase the duration of action and improve its safety profile compared with prostaglandin E ***(Collins et al., 1985).*** However the compound was still chemically unstable at room temperature the problem was solved through the dispersion of misoprostol in hydroxyl-propyl-methyl-cellulose***(Tang et al., 2007).***

Biosynthesis

Prostaglandins are released during allergic and inflammatoryprocesses. Activation of phospholipase A2 (which is present in cell membranes) causes the release of arachidonic acid, which is the primary precursor for prostaglandins from the phospholipid (***Rutgers, 2007).***

Next, the free acids are acted upon by one of two related enzymes, cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2). Both enzymes catalyse the same two reactions at different sites, i.e. a cyclooxygenase reaction in which two molecules of oxygen are added to arachidonic acid to form a bicyclic endoperoxide with a further hydroperoxy group in position 15, i.e. to form prostaglandin PGG2. The hydroperoxide is then reduced by a functionally coupled peroxidase reaction to form prostaglandin PGH2***(Christie, 2012).***

Functions of prostaglandins

There are a variety of physiological effects including:***(Ophardt, 2003):***

1. Activation of the inflammatory response, production of pain, and fever. When tissues sites are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.

2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2 is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.

3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGs cause uterine contractions and has been used to induce labor.

4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.

History of Misoprostol

Pharmaceutical companies first marketed prostaglandins in the 1970s.In 1988, the US Food and Drug Administration approved misoprostol under the brand name Cytotec®, for prevention of gastric ulcers among long-term users of non-

steroidal anti-inflammatory drugs***(Shannon &Winikoff, 2004).*** However, it was discovered that it affects the uterus as well as the gastrointestinal tract, so the US manufacturer warned against use of the drug by pregnant women ***(Briggs et al., 2006).***

In the United States, misoprostol is approved only for gastrointestinal indication, as well as in most countries, where misoprostol is not approved for obstetric or gynecologic indications. The notable exceptions are Brazil, Egypt, and France (***Burns et al., 2005).***

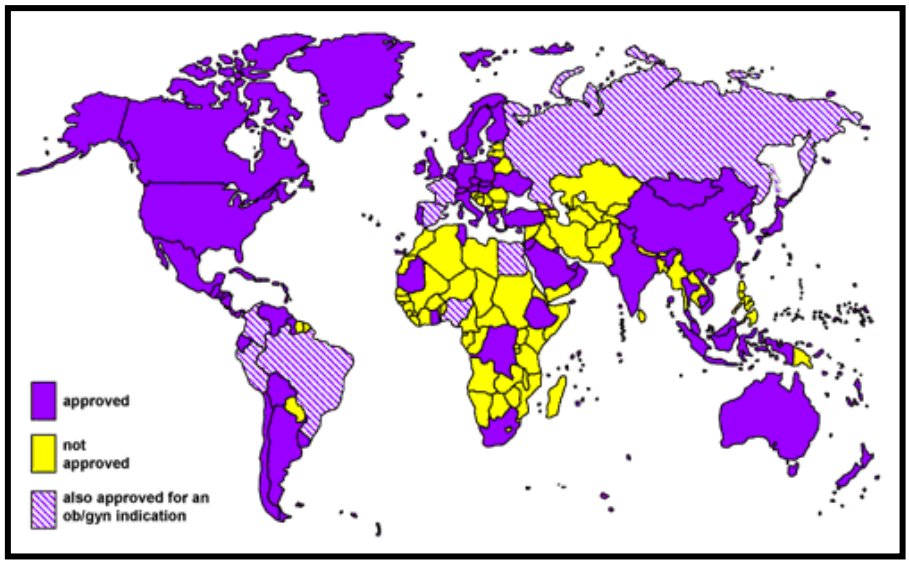


Figure (4): Countries where misoprostol is approved ***(Gynuityhealth project, 2009).***

Mechanism of Action

Being a prostaglandin E (PGE) analogue; misoprostol acts via interacting with PGE receptors.

There are four isoforms of the PGE receptor (EP1–4), which act through different intracellular pathways***(Arrowsmithet al., 2010):***

- EP1receptorscoupletocalciummobilizationand thus are uterotonins.
- EP3 receptors inhibit adenyl-cyclase and thus cAMP and Protein Kinase A. As both PKA and cAMP mostly relax the myometrium through a variety of mechanisms including decreasing Ca channel opening, phosphorylation of MLCK and stimulation of MLCP, EP3 will therefore be stimulatory.
- EP2 and EP4 stimulate cAMP thereby mediating relaxation.

The locations of these receptors are ***(Cleary, 2010):***

- EP1 & EP3 receptors are contraction promoting and are abundant in the fundus.
- EP2 & EP4 receptors are relaxation promoting and are found in lower uterine segment.

Pharmacodynamics

Misoprostol has both anti-secretory (inhibiting gastric acid secretion) and mucosal protective properties, so it has the ability to reduce the risk of peptic ulcer in patients taking NSAIDs by increasing bicarbonate and mucus production ***(Cytotec product information, 2009),***and is given in a dose of 800 micrograms daily in two or four divided doses ***(Doggrell, 2007).***

Misoprostol can also causemyometrial contractions by interacting with specific receptors on myometrial cells. This interaction results in a change in calcium concentration, thereby initiating muscle contraction. By interacting with prostaglandin receptors, so it causes the cervix to soften and the uterus to contract ***(Misoprost600 product information, 2010)***and also can lead to cervical ripening ***(Cleary, 2010).***

Pharmacokinetics

Naturally occurring PGE1 is not orally sustainable as it is unstable in acid media, also not suitable for parental use because of its rapid degradation in the blood, so synthetic PGE1 analogue has been produced by bringing alteration in chemical structure of this naturally occurring compound, thereby making it orally stable and useful ***(Burns et al., 2005).***

Misoprostol is an ester ***(Davies et al., 2001)*** that is rapidly and extensively de-esterfied to the active metabolite misoprostol acid (MPA) (***Doggrell, 2007)*** by the liver ***(Aronsson, 2007),*** and is excreted mainly in urine ***(Doggrell, 2007)*** with plasma elimination 20 - 40 minutes ***(Cytotec product information, 2007).***

Misoprostol acid is 85% bound to serum albumin plasma protein in a concentration-independent fashion ***(Davies et al., 2001).***

Pharmacokinetics of different routes of administration of misoprostol:

Over the last decade there have been a number of studies looking at the pharmacokinetic profile of various routes of administration of misoprostol ***(Tang et al., 2007).***

ORAL ROUTE:

When misoprostol is administered orally, it is rapidly and almost completely absorbed from the gastrointestinal tract (***Tang et al., 2007)***with bioavailability exceeds 80%, it is converted to the active misoprostol acid ***(More, 2002***) via extensive first-pass metabolism (de-esterification) (***Tang et al., 2007)***about 80% of it is excreted in urine ***(Cytotecproduct information, 2009).***

Studies showed that no accumulation of MPA was noted following 400 micrograms given at 12 hours intervals over 4 days and plasma steady state was achieved within 2 days, and maximum plasma concentrations of MPA are diminished when the dose is taken with food, and the total availability of misoprostol acid is reduced by concomitant use of antacid ***(Aronsson, 2007),*** however, this effect does not appear to be clinically important as shown in (Table 1) ***(Cytotecproduct information, 2009).***

Table (1): Effects of fasting, antacid and high fat meal on the pharmacokinetics of misoprostol

Mean ± SD	Cmax(pg/ml)	AUC(0-4) (pg.hr/ml) (pg-hr/ml)	Tmax(min)
Fasting	811 ±317	417 ±135	14 ±8
With Antacid	689 ±315	349 ±108	20 ±14
With High Fat Breakfast	303 ±176	373 ±111	64 ±79

SD=Standard deviation, **Cmax**=the peak concentration, **AUC** = area under serum concentration, **Tmax**=peak time concentration

(Cytotec product information 2009).

But unfortunately the oral route is accompanied by higher rates of gastrointestinal side effects ***(Allen and O'Brien, 2009),***to lessen the incidence of these side effects, misoprostol tablets have been administered by other routes specially when being used as uterine stimulant ***(Doggrell, 2007).***

VAGINAL ROUTE:

Vaginal misoprostol is associated with slower absorption, lower peak plasma levels, and slower clearance and greater effects on the cervix and uterus ***(Allen & O'Brien, 2009).*** It takes longer to start working, has a lower peak (peak concentration after 60 min), but a more sustained effect ***(Fiala et al., 2005).***

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 ***(Tang et al., 2007).***

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 (***Tang et al., 2007).*** These variations in absorption may be also due to cyclic changes in thickness of vaginal epithelium ***(Doggrell, 2007).***

Some studies showed that moistening of misoprostol tablets before vaginal administration improves its efficacy by improving the rate and extent of absorption ***(Doggrell, 2007),*** while other studies didn't find clinically significant difference between vaginal misoprostol that is administered dry and vaginal misoprostol moistened with water, saline, or acetic acid ***(Allen & O'Brien, 2009).***

Vaginal administration has advantages of reducing gastrointestinal side effects, with profound effect on reproductive tract***(Burns et al., 2005).***

SUBLINGUAL ROUTE:

Sublingual administration of misoprostol has been studied, and it was found that misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue***(Tang et al., 2007).***

Pharmacokinetic studies were done to compare the sublingual route to the oral and vaginal routes, and found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when