

Editorial

Misoprostol - A Wonder Drug

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Abstract

Misoprostol is a synthetic analogue of natural prostaglandin E1. It has a very convenient and flexible drug dosing, can be administered orally, sublingually, buccally, rectally and by vaginal route. Misoprostol is useful for elective early medical abortion, cervical ripening in surgical abortion as well as in gynecological D & C, mid trimester abortion, cervical ripening and induction of labour in live or dead fetus as well as in prevention and treatment of PPH.

Key words: Misoprostol, medical abortion, induction of labour, postpartum hemorrhage.

Introduction

Misoprostol is a synthetic analogue of natural prostaglandin E¹. It produces inhibition of gastric acid and pepsin secretion, and enhances mucosal resistance to injury. It is an effective anti ulcer agent and also has oxytocic properties.

Misoprostol was developed during 1980s and approved by FDA for the prevention of NSAID - induced gastric ulcers in 1988. Off-label exploration of the drug for obstetric purposes began soon after its development, and the drug has been studied extensively for a number of gynecological and obstetric indications.

Misoprostol is already included in the 14th and 15th edition of WHO MODEL List of Essential Medicines because of its proven safety and efficacy for medical abortion and labour induction¹. 17th Expert committee on the selection of and use of essential medicine in Geneva on March 2009 proposed the inclusion of misoprotol for prevention of PPH².

Misoprostol has a very convenient and flexible drug dosing, can be administered orally, sublingually, buccally, rectally and by vaginal route. Misoprostol is useful for elective early medical abortion, cervical ripening in surgical abortion as well as in gynecological D & C, mid trimester abortion, cervical ripening and induction of labour in live or dead fetus as well as in prevention and treatment of PPH.

The purpose of this article is to review the large body of evidences supporting the uses of misoprostol in pregnancy.

Pharmacokinetics

Misoprostol is a synthetic 15 deoxy-16 hydroxy-16 methyl analog of prostaglandin E1 and is water sol-

uble. The commercial preparations are available in tablets forms of 200 µgm and 100 µgm. 25 µgm tablets are now available in some countries. Misoprostol is rapidly absorbed by all routes of administrations but the most rapid action occurs when misoprostol is given orally (peak concentration after 12 min, half life 20-30 min). Misoprostol given vaginally or sublingually takes longer to start working, has a lower peak concentration after 60 min, but a more sustained effect. Thus, smaller doses are needed when misoprostol is inserted vaginally. Misoprostol is extensively absorbed, metabolized in liver and, undergoes rapid de-esterification to its free acid, i.e. misoprostol acid, which is responsible for its clinical activity and less than 1% of its active metabolite is excreted in urine³.

Mode of Action

Misoprostol causes uterine contractions and opening or ripening of cervix. Although prostaglandins (PGs) are highly effective, their efficacy depends on the number of PGs receptors in the uterus and this varies according to gestational age. In early pregnancy, there are few receptors and high doses of misoprostol may need to be given repeatedly in order have an effect. No problems have been reported in first trimester abortion with women who have had previous caesarean section⁴. The sensitivity of the uterus to misoprostol can be increased by giving the mifepristone (progesterone receptor blocker) 24-48 hours before misoprostol⁵. This is especially useful in early pregnancy, although it works in late pregnancy also. At term, there are many receptors and a small doses of misoprostol leads to strong contractions, so at term misoprostol cannot be used in women with previous caesarean as it may causes a

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ruptured uterus^{6,7}. A Meta-analysis by Plaut et al (1999) reported a 5.6% rate of rupture with the use of misoprostol compared with 0.2% in patient attempting vaginal birth after caesarean delivery with no stimulation⁶.

Adverse Reaction

Prolonged or serious side effects are rare. Side effects depend on the route, dose and the indications for which misoprostol is used.

Bleeding: Vaginal bleeding during abortion induced with misoprostol is generally more intense than regular menstrual bleeding and is usually no different from that which occurs with a spontaneous abortion⁸. The mean pre- to post-abortion fall in hemoglobin varies between 0.2 and 1.0 g/dL. Prolonged and intensive bleeding affects between 1% and 10% of women⁹ and may necessitate emergency surgical uterine evacuation, preferably with manual vacuum aspiration. The need for transfusion has been rarely reported. **Cramping:** Cramping usually starts within the first few hours and may begin as early as 30 min after misoprostol administration. The pain may be stronger than that experienced during a regular period and can be present in 80%-90% of women¹⁰. Nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesia can be used for pain relief without affecting the success of the method^{11,12}.

Fever and/or chills: Chills are a common side effect of misoprostol but are transient. Hyperthermia can be very severe¹³ and more common with higher doses or when the interval between doses is shorter or with oral or sublingual administration^{10, 14}. Fever does not necessarily indicate infection. An antipyretic can be used for relief of fever, if needed. If fever or chills persist beyond 24 h after taking misoprostol, the women may have an infection and should seek medical attention.

Nausea and vomiting: About 20% of women report pregnancy-related nausea and vomiting before treatment. These symptoms may increase after misopros-

tol administration. An anti-emetic can be used if needed, but symptoms will usually resolve within 2 to 6 h.

Diarrhea: Diarrhea may also occur following administration of misoprostol but usually resolve within a day.

Uterine contraction abnormalities: Induction of labour with misoprostol can cause uterine tachysystole in 10.1%, hypertonus in 10.7% and hyperstimulation syndrome in 13.8%¹⁵. There were no differences in the proportion of the subjects induced by oxytocin

Teratogenicity

The concerns about the medical safety of misoprostol emerged in early 1991 when the first case of fetal anomalies were reported in Ceara Brazil^{6,17}. The most common anomalies reported were limb defects followed by CNS anomalies, upper limb defects skeletal defects and other anomalies, such as defects of the genitalia, eyes and palate. Mobius syndrome, a rare condition characterized by the loss of function of the motor cranial nerves esp. (VI, VII & XII) is said to be associated with fetal misoprostol exposure¹⁸. A more commonly proposed mechanism of teratology involves vascular disruption caused by strong uterine contraction. One theory proposes that misoprostol induced contraction may bind the embryo in the area of cranial nuclei VI & VII, there by decreasing blood flow in the area, which results in hemorrhage and / or cell death in the cranial nuclei¹⁹.

Because estimates suggested that 5-10% of women exposed to misoprostol carried their pregnancies to term, risks of teratogenicity after failed abortion and continuing pregnancy were perceived to be high¹⁶. The relative risk of malformation appears real, epidemiological studies indicate the absolute risk is low and it is a mini teratogen means (less than 10 malformations per 1000 birth exposed to misoprostol in utero)²⁰.

Indications	Recommended Doses	Advantages & Efficacy	Remarks
Cervical ripening prior to uterine instrumentation	400µgm, vaginally or orally 3 hours before the procedure ²¹ .	less force needed for dilatation. It makes the intervention safer and easier. It shortens the time for procedure and may reduce the perforation and failure rates due to tight os.	Use for insertion of intrauterine contraceptive device, Surgical termination of pregnancy, Gynec dilatation & curettage, Hysteroscopy

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First trimester medical abortion	800 µgm vaginal or sublingually is given every 24 hours for 2 days	95-98.5% effective ^{22,23} . highly effective up to 63 day's LMP ²⁴ . FDA approved upto =49 days LMP	Misoprostol alone 800µgm vaginally 12 hrly X 2 doses ⁹ 75 - 85% effective upto 9 weeks of pregnancy ⁹
Incomplete abortion]	600 µgm orally single dose	95 - 100% effective ^{25,26}	Paracetamol or NSAIDS can be prescribed for pain due to uterine contraction. Bleeding may persist for upto 1 week. No need to reassess or intervenes unless heavy bleeding or infection.
Missed Abortion (upto 12 weeks gestation).	800 µgm vaginal or sublingually is given every 24 hours for 2 days	80 - 90% effective and usually no surgical intervention needed ^{27,28} .	Abdominal pain may occur. bleeding may persist for 1 weeks.
Missed abortion (12 - 24 weeks gestation) / Second trimester abortion	200 µgm vaginally is given every 12 hours until expulsion or 400 µgm orally every 4 hours until expulsion.	90 - 100% deliver in 48 hours. Some patient may need manual removal of placenta ^{29,30} Pre-treatment with mifepristone is especially useful in these cases.	Sometimes bleeding may be heavy, so blood should be arranged and sometimes requiring transfusion.
Induction of labour	25 µgm vaginally every 4 hours 31 X max. 6 doses or 50 µgm orally every 4 hours max 6 doses ³² .	For IUDS the dosages may be doubled if 2 doses have no effect. For this indication the misoprostol is best used 48 hours following mifepristone 200 mg where available ³³ .	Intravenous infusion of oxytocin should not be started until at least 4 hours following last dose. Contraindicated in previous scarred uterus. Misoprostol should not be repeated if 2 or more contraction in 10 minutes ³⁴ .
Induction of labour in premature rupture of membranes	100 µgm oral misoprostol every 6 hrs to max. 2 doses	have similar success in labour induction as oxytocin infusion ⁹ .	A recent WHO
Prevention of Postpartum hemorrhage	A single dose of misoprostol 600 µgm orally, administered immediately after delivery of the newborn, after confirming that there is no multiple pregnancy, and prior to the expulsion of the placenta ^{35,36} .		recommendation states, "In the absence of AMTSL*, a uterotonic agent (oxytocin or misoprostol may be administered by a trained in its use" ¹¹ .
Treatment of post partum heamorrhage.	A single dose of misoprostol 1000 µgm rectally or 200 µgm orally with 400 sublingually ^{37,38} .		It has no homodynamic side effects. 50% of women get shivering and the pyrexia usually 38-39 0C Misoprostol has both antisecretory & mucosal cytoprotective properties ⁴⁰ .
Topical application of misoprostol for wound healing	Shows promising result on animal study ³⁹		It also increase tissue collagen level without influencing inflammation ⁴¹ .

(*AMTSL- Active management of third stage of labour)

Conclusion

Misoprostol is one the most important medication in obstetrical practice. In April 2002, the FDA finally approved a new label for the use of misoprostol during pregnancy⁴².

Misoprostol is now a legitimate part of the FDA approved regime for use with mifepristone to induce abortion in early pregnancy and is also recognized for its use for induction of labour⁴³.

The increased access to and information on the use of misoprostol could help to improve women's health and decrease the morbidity and mortality associated with various obstetrics and gynecological conditions.

Misoprostol is a wonderful drug as it can be used in all trimester of pregnancy by all routes except injectable in living or dead fetus with simple dose schedule and minimum side effects. Its potential is especially promising in the developing world where maternal mortality is high and where an effective,

low cost and stable prostaglandin is urgently needed. The benefits of misoprostol in settings with few resources have since been widely demonstrated. It has facilitated difficult challenge of evacuating a dead fetus during the second trimester of pregnancy, substituting methods that carry a high risk of morbidity and mortality⁴⁴. It has also proved its efficacy to prevent PPH in situation where oxytocin is not available or lose its effectiveness due to high ambient temperature⁴⁵. There is also now evidence to correlate the increase its use with reduction of morbidity and mortality associated with abortion in countries with restrictive laws⁴⁶.

Over the year a drug was required which could prevent PPH in periphery and can be used by trained birth attendant, which is the need of our country, so we can call it a wonder drug

With the help of this article, it is hoped that dangerous misuse will be avoided and practice may be improved with a view to reduce maternal morbidity and mortality.

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