REVIEW ARTICLE

UPDATE ON MISOPROSTOL

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ABSTRACT

Misoprostol, a drug primarily developed for the treatment of peptic ulcer is now being widely used for ever increasing indications in obstetrics and gynaecology due to its uterotonic action. The drug has come a long way following off label use and warning from manufacturers and FDA. Initially introduction of drug led to a flurry of adverse reports due to publication bias and also the fact that optimal dose and route was yet to be determined. There are more randomized controlled trials on use of this novel drug compared to any other drug in obstetrics and gynaecology. Finally after federal drug agency (FDA) approval in USA and recommendation the drug is used widely. Due to low cost, ease of storage and multiple routes of administration – oral, sublingual, vaginal and rectal uptake was very rapid. Misoprostol has changed the face of 1st trimester medical termination an also 2nd trimester induction. As an alternative to dinoprostone the safety of the drug has been validated along with great cost savings. Except for prophylaxis of post partum haemorrhage where the drug was less effective compared to counterparts there is evidence in favour of misoprostol for all other indications.

Keywords: Misoprostol, labour induction, Post partum haemorrhage.

BACKGROUND

Misoprostal (Cytotec) 15deoxy 16 hydroxy 16 CH3PGE1 was the first synthetic analogue to be made available for the treatment of peptic ulcer and it was licensed for this condition in over 80 countries. Impressed by its stimulant action on uterus Sanches Ramos in 1993 used it for obstetric indications [1]. Although not formally registered for use during pregnancy many countries allow licensed drugs to be used for other indications.

It acts on the uterus and causes contraction of smooth muscle fibres and softening of cervix. This in turn facilitates intrauterine procedures as well as expulsion of contents of the uterus [2].

Pharmacokinetics: After oral administration plasma concentration increase rapidly to a peak at 30 min and then declines rapidly. Vaginal administration increases plasma levels gradually and reaches a peak at 11/2 hour before declining steadily prolonging the effect via this route [3].

Dosage and administration: It is stable at room temperature and does not require refrigeration [4]. The cost is Rs 50.00 for 200 ugm tablet of cytotec. This is tremendously low compared to Prostaglandin E2 which is about Rs: 800.00 for a 3mg tablet. Oral route seems to be as effective as vaginal for cervical ripening. Sublingual route is another route of administration with higher rates of tachysystole [4]. Like oral the levels increase to high levels for a short time. Induction of labour earlier with vaginal than oral but previous studies show a higher rate of tachysystole [5]

Moistening was 1st investigated by Ngai [6]. They showed that efficacy can be improved from 60-90% by moistening.

Adverse Effects: Nausea, vomiting, abdominal pain, fever and chills are known side effects. Diarrhea is the commonest side effect.

Vaginal administration requires repeated examination which is inconvenient and unacceptable to some patients. Incomplete abortion following misoprostol can lead to prolonged and profuse bleeding.

Exposure during conception can lead to teratogenicity in the 1st trimester. This manifests as vascular abnormalities defective formation of frontal and occipital bones [7, 8]. It is also linked to autism [9].

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In women with previous caesarean section there is higher frequency of scar disruption [10].

Indications in Obstetrics and gynaecology:

The indications are ever increasing and include

- Termination of pregnancy

1st trimester

2nd trimester

Cervical ripening prior to surgical abortion

- Uterine evacuation

Missed abortion, intrauterine contraceptive devise retrieval and incomplete abortion

- Labour and delivery: Cervical ripening for induction of labour, prophylaxis and management of post partum haemorrhage.

Cervical softening: for mirena/pipelle

We will now discuss the indications one by one.

Termination of pregnancy:

1. 1st trimester: Non viable or unwanted pregnancy can be terminated using misoprostal with or without mefepristone. Mefepristone leads to shorter induction to abortion interval. However mefepristone is not available in many developing countries. It only marginally increases the success rate in early pregnancy less than 42 days .Wagarachi et al 83% success rate with increased incidence of side effects following sub-lingual use [11]. The same group reported decreased side effects when 1st dose was vaginal without undermining the success rate. El-Rafey reported 93% success rate following 2 days of oral use [12]. The incidence of side effects were higher compared to vaginal with 5% need for readmission and 25% need for analgesia.

According to royal college of gynaecologists (RCOG) guideline no 25 for 1st trimester 800ugm misoprostol should be administered by a clinician or self administered by the woman [13]. If abortion does not occur in 4 hours a 2nd dose of 400ugm may be given orally or vaginally depending on patient preference or amount of bleeding. A maximum of 4 doses of misoprostol 400ugm may be administered orally or vaginally at 3 hourly intervals. Facilities for immediate D& E (dilatation and evacuation) should be available in the event of excessive vaginal bleeding. According to Carbonal et al vaginal misoprostol medical therapy for early pregnancy failure is effective & well accepted [14]. It avoids the cost and potential complications of surgery and increases patient satisfaction. The results of WHO multinational trial on 3 drug regimens showed that oral is associated with higher frequency of nausea /vomiting compared to vaginal [15]. Lower abdominal pain was similar in both groups. Should a need arise most women would choose medical abortion again and would prefer clinic to home abortion.

Incomplete miscarriage: Medical management of incomplete miscarriage has fewer side effects but the success rate is 50-60% compared to 98% for surgical management. Recommended dose is 400ugm 4 hourly upto 4 doses.

2. Second trimester: For midtrimester abortion mefepristone if available misoprostol merits grade B recommendation as an alternative to dilatation and evacuation according to RCOG guideline [13]. In a country like Pakistan where labour induction is the norm at gestation>15 weeks, misoprostol has changed the face of mid trimester abortion by shortening induction to abortion time. The dose recommended by Royal college guideline is similar to that in the 1st trimester.

The side effect in study by Grimes et al like pain and preabortion bleeding are more for misoprostol compared to dilatation and evacuation but these are not serious. The use of sublingual misoprostol for middle trimester miscarriage is a safe alternative depending on patient preference [16].

Cervical Ripening and Induction of labour at term: Induction of labour in a primigravida with an unfavourable cervix is a major challenge.

Misoprostol 50ug vaginal compared to 3mg dinoprostone leads to shorter induction to delivery intervals. Search for safe and inexpensive labour inducing agents led to a flurry of reports advocating the use of either oral or vaginal misoprostol for induction of labour at term [17]. Because of its low cost and wide availability it is adopted in third world for labour induction. A systemic review comparing 50ugm versus 25ugm for labour induction showed that former had short induction to delivery interval but slightly higher incidence of uterine hyperstimulation [18, 19].

Oral misoprostol 100ugm 4 hourly compared to vaginal dinoprostone has been shown to have equal efficacy but higher rate of uterine tachysystole that did not translate into adverse fetal or maternal outcome, but would have to be monitored carefully [20, 21].

Recently the large UK multicentric open label trial showed that low dose misoprostol had efficacy and safety similar to dinoprostone. The trial used a specially designed tablet rather than a crushed one. The cost in a UK set up is reduced by 22 pounds per induction where misoprostol replaces dinoprostone [22].

100ugm oral compares with 25ugm vaginal in most trials .50ugm sublingual route may have the same efficacy and safety as 100ugm oral which has been explored by the same author in Aberdeen [23]. These small studies need revalidation by other investigators.

USA Food and Drug administration has approved a new off label use for misoprostol. They recommend the 25ugm dose 6 hourly. Oxytocin should not be given within 4 hours of misoprostol.The dose continues regarding the optimal dose regimen and route.

A placebo controlled trail of oral 100ugm misoprostol for prelabour ruptured membranes showed that misoprostol significantly reduced the use of oxytocin and induction to delivery interval [24]. Oral misoprostol also reduced the number of vaginal examination and risk of chotioamnionitis [25].

Misoprostol safety issues for induction of labour at term Occasional case of uterine rupture continue to be reported with 100ugm or 50ugm doses26. There may well be a publication bias. Meconium is passed more frequently with misoprostol than dinoprostone due to difference in transplacental passage of drugs [27].

Third stage of labour: In less than 8 years of use of misoprostol 20 randomized controlled trials have been publish regarding its role in postpartum haemorrhage (PPH). This is in sharp contrast to oxytocin where there are less than 10 in 30 years [28, 29].

Prevention of PPH: Despite the hopes pinned down to misoprostol as to the answer to PPH in developing countries oral and rectal misoprostol were found not to be as effective as conventional injectable uterotonic agents High rates of shivering and fever make it undesirable for routine use in low risk women. WHO large multicentric trial on 18000 patients on misoprostol for third stage of labour fueled the controversy rather than settling it [30]. The trial showed increase in blood loss in misoprostol arm but blood transfusion admission to intensive care was more in oxytocin arm. A further systemic review by the WHO team showed that misoprostol should not replace conventional uterotonic agents. Danny;s commentary in Lancet says that the lesser efficacy is due to late peak and this problem could be solved by sublingual route [30].

Treatment of PPH: Evidence here is robust. A Cochrane data base review review suggests that rectal misoprostol in a dose 800ugm would be useful as 1st line drug for management of PPH. Further randomized controlled trials are in progress to determine the best route, dose and drug combination [31].

Off-label use of misoprostol: Clearly many drugs with proven efficacy are not liscenced. A physician has a legal right to prescribe off label as long as his practicing habits are based on sound scientific knowledge. In response to adverse case reports and to protect itself from litigation Searle the manufacturer of

misoprostol (cytotec) in Aug 2000 advised against off-label use of cytotec [32]. This led to restriction of drug to formal research protocol. In 2002 FDA approved major changes to cytotec labeling which recognizes off label use and provides safety information for the patients [33, 34].

CONCLUSION

Misoprostol has drawn an emotive debate in the literature from the camps of antiabortion lobby, manufacturer Searle, American College of Obstetrians and Gynaecologists (ACOG), misoprostol enthusiasts and skeptics. Due to its effectiveness, low cost, stability in light and hot climate and ease of administration it has been used widely in obstetrics and gynaecology. The drug may lead to abuse which may have disastrous consequences. An exhaustive search of literature shows only one maternal death associated with cytotec due to uterine rupture.

With proper guidelines and education misoprostol can be safely used in the existing setting by qualified practitioners in selected patients and see how it will influence their clinical practice depending on priorities of their own clinical circumstances.

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