Overview of Misoprostol and Hyoscine Butylbromide as a Cervical Priming Agent Prior to Hysteroscopy

Marwa Ahmed Elsayed, Ashraf Talat Abd Elfatah, Hala Sherif Elsayed, Ahmed Ismail Mohamed

Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Marwa Ahmed Elsayed ,

drmarwaahmedobgyne@gmail.com

ABSTRACT

Hysteroscopy is a minimally invasive intervention that can be used to diagnose and treat many intrauterine and endocervical problems. Hysteroscopic polypectomy and myomectomy are just a few of the commonly performed procedures. Given their safety and efficacy, diagnostic and operative hysteroscopy have become standards in gynecologic practice.Operative hysteroscopy is best performed after menstrual flow has stopped in the proliferative phase of the menstrual cycle because it is when the endometrium is thin. We can also achieve that by inducing endometrial atrophy by using different drugs such as progestins, combined oral contraceptive pills, gonadotropin-releasing hormone agonist, or danazol. There is no rule for using prophylactic antibiotics routinely for most hysteroscopic procedures because postoperative infection rates are low.Misoprostol, a prostaglandin E1 analog, which was initially used for the treatment of peptic ulcers, has been widely applied in obstetrics and gynecology because of its ripening effect on cervix during the induction of abortion or labor. Hyoscine-n-butyl bromide (HBB) is a peripheral anticholinergic and does not readily cross the blood-brain barrier.The effects of misoprostol or Hyoscine Butylbromide use on cervical priming prior to hysteroscopy have been controversial. The aim of the present study was to review the using of misoprostol or hyoscine butylbromide as a cervical priming agent prior to hysteroscopy.

Keywords: Hysteroscopy; Misoprostol; Hyoscine Butylbromide

INTRODUCTION

Hysteroscopy has revolutionized the field of Gynecology and the management of many gynecological conditions. It has now become a standard part of the gynecologic surgeries. Cost, convenience, accuracy, and patient acceptability of these procedures are clearly superior to those of traditional surgeries. As gynecologists have grown better with the benefits and techniques of operative hysteroscopy, it has become the method of choice for treatment of intrauterine pathology **(1)**.

Between the 1970s and 1980s, the modern hysteroscopic approach was reported by various authors. For the next 10 years or more the cervix and the uterine cavity were examined using a diagnostic hysteroscope with a total diameter of 5 mm, consisting of a 4-mm rod lens system scope inserted in a simple sheath, necessary to guide the distention media (CO_2) into the uterine cavity **(2)**.

Hysteroscopy is the process of viewing and operating in the endometrial cavity from a transcervical approach. The basic hysteroscope is a long, narrow telescope

connected to a light source to illuminate the area to be visualized. A camera is commonly attached to the proximal end of the hysteroscope to broadcast the image onto a large video screen. Other common modifications are inflow and outflow tracts included in the shaft of the telescope for fluids. A distending media, a fluid or carbon dioxide , can be pumped through a hysteroscope to distend the endometrial cavity, enabling visualization and operation in an enlarged area **(**3**)**.

Diagnostic hysteroscopy is an intrauterine examination without the expectation of a therapeutic intervention. Accurate knowledge of the position of the uterus is critical to facilitate the examination **(4).**

The best time to perform a diagnostic hysteroscopy is during the proliferative phase of the menstrual cycle. The patient is placed in lithotomy position and perineum and vagina prepared with povidone iodine. Sims retractor retracts the posterior vaginal wall and the cervix is visualized. The cervix is grasped with a single toothed tenaculum. The telescope is assembled and checked for clarity of image. The distention media flow is started as the hysteroscope is engaged into the external os of the cervix **(4).**

Cervical dilatation is not required in multiparous women, whereas some dilatation may be needed in nulliparous women. Excess dilatation is avoided to prevent escape of the media from the sides of the telescope. As the endoscope is advanced through the external os, the distention media separates the wall of the endocervix to allow excellent view of the endocervical folds and crypts Flow rate might need adjustment after entering the uterine cavity **(5).**

Systematic examination of all four walls of the uterine cavity and the tubal openings is carried out with axial movements of the telescope. The endometrium is smooth and pink white in color during the proliferative phase and lush and velvety in the secretory phase. Any abnormal pathology should be documented. This procedure can be done on an outpatient basis with or without anesthesia **(5).**

Diagnostic hysteroscopes of small caliber (<5-mm outer diameter) can be of two types: rigid and flexible. The rigid endoscopes have wide-angle optics and excellent resolution. The telescope has a 3- to 4-mm outer diameter, and the encasing sheaths a 4- to 6-mm outer diameter. Although all endoscopes of <3-mm outer diameter encased in a 4-mm outer diameter sheath seldom require cervical dilatation, when this diameter increases, some type of dilatation may be required **(1)**.

- **Misoprostol :**

Misoprostol is a synthetic prostaglandin E1 analog which contains approximately equal amounts of the two diastereomers presented below with their enantiomers **(6).**

Misoprostol tablets were formed to be used orally. Other routes of administration including vaginal, sublingual, buccal and rectal**.** There are three pharmacokinetic properties, the peak concentration, time to peak concentration and the area under the serum concentration versus time curve were studied. 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 **(7).**

Misoprostol can be given orally, sublingually, vaginally or rectally, as the bioavailability varies with each route, the route of administration will be preferred according to the patient and the clinical situation .If there is vaginal bleeding or loss of amniotic fluid, oral or sublingual route is preferable in these cases due to negative effect on vaginal absorption. Also most women prefer the oral route to vaginal application **(8).**

Misoprostol is absorbed rapidly and completely through gastrointestinal tract. It undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid. Following a single dose of 400 μg oral misoprostol, the plasma misoprostol level increases rapidly and peaks at about 30 minutes, declines rapidly by 120 minutes and remains low **(9).**

In contrast to the oral route, the plasma concentration increases gradually after vaginal administration, reaching its maximum level after 70-80 minutes, then decline slowly and drug levels still present after 6 hours **(10).**

Vaginal misoprostol has great bioavailability; it is more effective in medical abortion. It has been shown that the vaginal absorption of misoprostol is inconsistent. In clinical practice, remnants of tablets are sometimes seen many hours after vaginal administration, indicating that the absorption is variable and incomplete .Amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal mucosa **(10).**

Sublingual administration of misoprostol has been studied for the cervical priming. The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. A pharmacokinetic study compared the absorption kinetics of oral, vaginal and sublingual routes of administration of misoprostol. It found that the sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes **(11).**

Misoprostol has been on the market under the brand name of Cytotec®. It is now available in over 80 countries worldwide for the treatment of gastric ulcer after treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Many scientific articles have been published showing the usefulness of misoprostol in obstetrics and gynecology. Now other brands licensed for22 use in pregnancy (e.g. misoprostol tablets from IVAX, Gymiso and Vagiprost®).Another brand name is Arthrotec® containing 200μg of misoprostol and 50- 75mg of diclofenac. One tablet of Arthrotec® plus the remaining dose given as Cytotec will therefore include already a prophylactic pain treatment **(12).**

Uses of Misoprostol:

1. Ulcer prevention:

Misoprostol is primarily used to prevent or treat gastrointestinal injury or blood loss related to non-steroidal anti-inflammatory drug (NSAID) ingestion. It is used in patients with arthritis who have to continue taking NSAIDs despite of suffering from

peptic ulcer that refuses to respond to histamine blockers. The drug promotes healing of these ulcers. Some patients on NSAIDs should receive misoprostol as elderly individuals, patients who are unable to tolerate ulcer complication, Patients receiving steroid therapy, those receiving high dose of NSAIDs **(13).**

2. Cervical Ripening Prior to Uterine Instrumentation:

It reduces the need for rapid mechanical dilatation of the cervix which lead to cervical laceration with immediate morbidity, and the possibility of remote complications such as cervical incompetence **(14).** Some studies which compared the use of vaginal misoprostol versus placebo dose have determined that 400 ug vaginal misoprostol, given 3-4 hours prior to the procedure, is probably the optimal treatment for achieving adequate dilation in over 95% of women prior to suction evacuation **(15).**

3. First Trimester Medical Abortion:

Medical abortion has become an alternative method of first trimester pregnancy termination with the availability of prostaglandins in the early 1970s and anti-progesterone in the 1980s. Studies on the use of misoprostol alone for first trimester medical abortion have largely been unsatisfactory. Repeated doses were required and it took a few days for the effect to complete. The overall successful rate ranged from 40-90% (**16).**

Sublingual administration is less effective than vaginal administration unless it is given every 3 hours, but this regimen has high rates of gastrointestinal side effects, Oral administration is not recommended due to low efficacy **(17).**

4. Second trimester medical abortion

Induction of abortion after 14 weeks of gestation is associated with a sharp rise in the rates of complications and in the consequent medical costs. Medical abortion using prostaglandin analogues alone or in combination with mifepristone has been proven to be effective for second trimester abortion and the termination of pregnancy with intrauterine death (**17).**

5. Treatment of postpartum hemorrhage:

Misoprostol has been used both as prevention and treatment of postpartum hemorrhage secondary to its uterotonic properties, oxytocin and methylergotomine are available as part of the management of the third stage of labor (**18).**

Assessment of the incidence of genital tract bleeding associated with vaginal prostaglandins before hysteroscopy it was found that there is no increased risk with the use of prostaglandins **(19).**

Numerous studies indicated the efficacy of misoprostol for achieving cervical dilatation in patients undergoing hysteroscopy. On other hand, the discrepancy may be due to small sample sizes, differences in the route of administration of misoprostol, the

types of hysteroscopy (operative or diagnostic hysteroscopy), and/or different populations under study **(20)**.

Hyoscine butylbromide:

Hyoscine butylbromide (HBB) was discovered in 1950, and approved for medical use in 1951. Is on the World Health Organization's List of Essential Medicines. It is manufactured from hyoscine, which occurs naturally in the plant deadly nightshade. it is an anticholinergic medication used to treat abdominal pain, esophageal spasms, bladder spasms, renal colic. Hyoscine butylbromide can be taken by mouth, injection into a muscle, or into a vein **(21).**

Hyoscyamine is a tropane alkaloid, purified from the leaves of the Solanaceae plant species, specifically the Duboisia plant, native to Australia .A levorotatory isomer of atropine, hyoscyamine is converted into hyoscine (also known as scopolamine) following a two-step process involving epoxidation. An N-group butylbromide addition to hyoscine produces HBB, a molecule which has properties comparable to those of hyoscine, but with poor systemic absorption, improving the safety profile of HBB when compared with the precursor molecule **(22).**

Hyoscine butylbromide reduces smooth muscle contraction and the production of respiratory secretions. These are normally stimulated by the parasympathetic nervous system, via the neurotransmitter acetylcholine. As an antimuscarinic, hyoscine butylbromide binds to muscarinic acetylcholine receptors, blocking their effect **(23).**

Hyoscine butylbromide is effective in treating crampy abdominal pain **(22).** HBB is effective in reducing the duration of the first stage of labour, and it is not associated with any obvious adverse outcomes in mother or neonate **(20) .**

It is also used during abdominal, pelvic MRI, virtual colonoscopy, and double barium contrasted studies to improve the quality of pictures[Hyoscine butylbromide can reduce the peristaltic movement of the intestines and mucosal foldings, thus reducing the movement artifact of the images **(22).**

Since little of the medication crosses the blood brain barrier, this drug has less effect on the brain and therefore causes a reduced occurrence of the centrally-mediated effects (such as delusions, somnolence and inhibition of motor functions) which reduce the usefulness of some other anticholinergic drugs. Hyoscine butylbromide is still capable of affecting the chemoreceptor trigger zone, due to the lack of a well-developed blood-brain barrier in the medulla oblongata, which increases the antiemetic effect it produces via local action on the smooth muscle of the gastrointestinal tract **(23).**

Other side effects include accommodation reflex disturbances, tachycardia, dry mouth, nausea; urinary retention, reduced blood pressure; dyshidrosis; Other symptoms are dizziness, flushing and immune system disorders (anaphylactic shock, potentially fatal); anaphylactic reactions; dyspnoea; skin reactions and other hypersensitivity reactions. Cautions should be taken for those with untreated

glaucoma, heart failure; benign prostatic hypertrophy with urinary retention as hyoscine may exacerbate these conditions **(24).**

CONCLUSION:

Hysteroscopy is potentially useful for female sterilization and offers promise as an investigative tool for studying the intratubal milieu.

Misoprostol was a cervical priming agent before hysteroscopy and surgical abortion**.** The recommended misoprostol regimen is 800mcg administered vaginally or sublingually, and repeated at intervals no less than 3 hours.

Misoprostol or Hyoscine butylbromide prior to hysteroscopy may facilitate cervical dilatation. Hyoscine butylbromide reduced the need for pain medication

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