A Randomized Controlled Trial of Evening Primrose Oil for Cervical Priming Prior to Operative Hysteroscopy

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Objective: The purpose of this study was to determine the efficacy of Evening Primrose Oil as a cervical ripening agent when used prior to operative hysteroscopy. **Study Design**: A randomized, double-blind, placebo-controlled trial included a total of 42 patients randomly assigned to the Evening Primrose Oil group (24) and to the placebo group (18). The primary outcome was initial cervical dilatation prior to hysteroscopy. The number of patients requiring cervical dilatation and duration of cervical dilatation to Hegar dilator size 10 were included as secondary outcomes. **Results**: There was a statistical and clinically significant difference between the initial cervical dilatation in the treatment and placebo groups (7.81mm vs. 4.33mm). All patients in the placebo group required cervical dilatation prior to hysteroscopy while only 47.62 percent of patients in the treatment group required any dilatation. It took an average of 53.56 seconds to dilate the cervix to Hegar size 10 in the placebo group compared to 17.43 seconds in the treatment group. **Conclusion**: Similar to trials in pregnant patients, this study proved that Evening Primrose Oil can be used as a cervical priming agent prior to gynecologic procedures.

Key words: evening primrose oil, cervical priming, hysteroscopy

Introduction

Operative hysteroscopy has gained popularity over the past decades as a minimally invasive approach to intrauterine lesions.[1] Hysteroscopy permits a panoramic view of the uterine cavity, thus increasing the accuracy of diagnoses and efficacy of resection or ablation of endometrial lesions. Cervical dilatation represents a real challenge during hysteroscopy.[2] Difficulty in cervical dilatation, particularly in operative hysteroscopy, is the most common cause of complications such as cervical tears, creation of false tracts and uterine perforation.[3] The incidence of such complications may be reduced with adequate preparation of the cervix prior to hysteroscopy.

Trials of cervical priming prior to hysteroscopy started as early as 1985 wherein intracervical sulprostone gel was applied which lead to a significant reduction in force needed to dilate the cervix.[1] We have come a long way since then. Today, safer and more convenient methods of cervical priming are being utilized in gynecologic procedures. Misoprostol is a synthetic prostaglandin E1 analogue widely prescribed for the prevention and treatment of gastric ulcers.[4] It is cheap and associated with few gastrointestinal side effects. It has been shown to have cervical priming effects on both pregnant and non-pregnant women whether administered orally or vaginally.[2,3,5,6] However, in House Bill 4643, misoprostol has been cited as an abortive drug and any physician, midwife, nurse and health worker who will prescribe or administer it, will suffer the penalty of 12 years of imprisonment and revocation of license.

Laminaria tents are made from the stems of *Laminaria japonica* (brown sea weed) and in its dry form, it absorbs fluid from the cervix facilitating cervical dilatation.[1] Vaginal insertion of laminaria has been shown to be effective in priming the cervix with minimal local and no systemic side effects. However, it is costly and not readily available. Although cervical dilatation is achieved by the use of laminaria, the consistency of the cervix is still firm, compromising the ease of the procedure.

Taking this into consideration, there is a need for another effective, safe and affordable cervical priming

agent which can be used in non-pregnant women in general gynecologic practice.

Several medications are currently being studied in relation to cervical priming for labor induction and gynecologic procedures.

Hyoscine (also known as scopolamine) butylbromide is a quaternary ammonium derivative, which exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary, and genitourinary tracts. Oral, rectal and intravenous administration of this drug has been studied in cervical priming in pregnant patients.[7] The use of hormonal agents including estrogen and progesterone as cervical priming agents have been studied as well. Progesterone has a weak cervical priming effect while estrogen priming in combination with misoprostol is effective in softening the cervix of postmenopausal women.[8,9]

Evening Primrose Oil is a standardized extract obtained from the seeds of the plant, *Oenothera biennis*.[10] It contains an omega-6 essential fatty acid, gamma-linoleic acid (GLA), which is believed to be the active ingredient. Evening Primrose Oil has been studied in a wide variety of disorders, particularly those affected by metabolic products of essential fatty acids. However, high-quality evidence for its use in most conditions is still lacking. Reports attribute many positive effects to Evening Primrose Oil including stimulation of cervical ripening, premenstrual syndrome symptom relief, treatment of obesity, diabetic neuropathy, numerous skin conditions as well as improvement in chronic autoimmune diseases such as rheumatoid arthritis, Raynaud's syndrome, Sjogren's syndrome, and multiple sclerosis.[10] There are only a few studies done both in foreign and local settings involving Evening Primrose Oil in cervical ripening. In 2004, Ty-Torredes, et al. reported that Evening Primrose Oil of 1000mg given thrice daily for 1 week had a significant effect on the Bishop score and cervical length as assessed by transvaginal ultrasound compared to placebo. They also reported no adverse effects on the mother and fetal safety profile.[11] A study on the use of Evening Primrose Oil by Macfarlin, et al. in 1999 showed that 60 percent of certified nurse-midwives in the United States used the dietary supplement to stimulate labor.[12]

At present, the handful of studies involving Evening Primrose Oil for cervical ripening have only been compared to placebos and tested only on pregnant patients. The effect of Evening Primrose Oil on non-pregnant patients for gynecologic procedures has yet to be explored.

Significance of the Study

This study aims to focus on an alternative preoperative measure in cervical priming in an effort to prevent complications associated with operative hysteroscopy.

Objectives of the Study

General Objective

To determine the efficacy of Evening Primrose Oil as a cervical ripening agent when used prior to operative hysteroscopy.

Specific Objectives

1. To determine the efficacy of Evening Primrose Oil versus placebo as a cervical priming agent prior to hysteroscopy with respect to the following:
   a. Initial cervical dilatation prior to hysteroscopy (mm)
   b. Number of patients requiring cervical dilatation

2. To determine efficacy of Evening Primrose Oil versus placebo as a cervical priming agent with respect to the following technical characteristics:
   a. Subjective ease of cervical dilatation
   b. Duration of cervical dilatation to Hegar size 10 (seconds)

3. To compare the following postoperative characteristics of the patients given Evening Primrose Oil with patients given placebo:
   a. Postoperative pain assessment
   b. Adverse events
   c. Complications associated with the procedure

Materials and Methods

This is a randomized, double-blind, placebo-controlled trial. The primary outcome was initial cervical dilatation prior to hysteroscopy.

The study was conducted at the Philippine General Hospital. The target population was all inpatient women undergoing operative hysteroscopy for intrauterine lesions diagnosed by saline infusion sonography done on day 8 to day 10 of menstruation.

Reasons for exclusion were pregnancy, lactation, genital tract infection, dilated cervix due to a prolapsed intrauterine lesion, patients with mullerian anomalies, history of cervical surgery or cervical incompetence, known allergy to the cervical priming agent or placebo, patients with diabetes mellitus, liver and renal disease, and previous treatment with gonadotropin releasing hormone (GnRH) agonist.

The calculation of sample size was based on an estimation that was enough to detect a difference of 3.3 mm in cervical width between the cervical priming agent and the placebo. Fifteen subjects were needed in each arm to detect a type I error of 0.05 with a power of 0.95.

Out-patient medical records of women presenting with intrauterine lesions diagnosed by ultrasound were screened for eligibility to participate in the trial. Candidates for the trial were approached by a fellow of the Department of Obstetrics and Gynecology and were given detailed information regarding the study. A detailed history and thorough physical examination were done on prospective participants. They were also asked to sign a consent form approved by the bioethics board. Returning eligible patients were randomly allocated to the Evening Primrose Oil or placebo group according to a table of computer generated random numbers. The numbers corresponded to sealed envelopes that indicate whether Drug A or Drug B should be given. The participants, their caregivers and researcher were blinded as to the type of intervention given. Patients assigned to the Evening Primrose Oil group were given 1000 mg of oral Evening Primrose Oil and those assigned to the placebo group were given 300 IU of d-alpha tocopherol (Vitamin E). Vitamin E was used as placebo because it has no known toxic or adverse effects. It resembles Evening Primrose Oil soft gel capsules and it has no cervical priming effects. Laminaria tents were not used in the control group because of several reasons: 1) it is costly, 2) it is not readily available and 3) blinding of the subjects, and researcher would not be possible since the route of administration is vaginal and not oral. Misoprostol, on the other hand, is considered an illegal drug and can not be used in the study. Patients were instructed to take their assigned medications starting 7 days prior to the procedure at a dose of three times a day for 7 days. A repeat transvaginal sonography was done prior to the operative hysteroscopy. The endometrial lesion and endometrial thickness were assessed. Hysteroscopy was timed at the proliferative phase of the menstrual cycle. All operations were done by any of the 6 fellows of the Endoscopic Unit with comparable level of experience. The randomization was unknown to the surgeon.

Primary outcome was cervical dilatation in millimeters prior to hysteroscopy as measured by the maximum calibre Hegar dilator that could be inserted into the cervix without resistance. A 0 degree hysteroscope with a 10 millimeter operative implement was used. Secondary outcomes include number of patients requiring cervical dilatation, subjective ease of cervical dilatation recorded on a Likert scale as assessed by the surgeon and duration of cervical dilatation to Hegar dilator size 10. Postoperative pain and complications associated with the procedure as well as adverse effects of the cervical ripening agent and placebo were also considered. Other variables assessed included age, nulliparity, pre and postmenopausal status, reasons for consult and history of infertility.

Demographic and clinical characteristics were described [mean, standard deviation (SD) and minimum-maximum values were reported for quantitative variables, absolute and relative frequencies were reported for categorical variables] according to the treatment group. Independent t-test was used to test the null hypothesis that there is no difference between the Evening Primrose Oil and placebo against the alternative that there is a difference for the following variables: 1) initial cervical dilatation, 2) subjective ease of cervical dilatation, 3) duration of cervical dilatation, and 4) postoperative pain measured by a Visual Analog Scale. Likewise, the 95% confidence intervals of the differences between the two groups with respect to these variables were reported. The percentage of patients who required cervical dilatation was reported for the two groups. The difference was estimated at a 95% confidence level.

Results

A total of 56 patients were screened for eligibility, 42 were randomized, 24 in the Evening Primrose Oil group and 18 in the placebo group. In the Evening Primrose Oil group, one (1) patient voluntarily withdrew, 1 failed to come back for follow-up and another required additional treatment and was eventually excluded. Table 1 shows the demographic and baseline clinical characteristics of both groups. The patients in the placebo group were older by 2 years on the average. Majority of the patients in the Evening Primrose Oil group underwent hysteroscopy for endometrial polyps (75%). There was no significant difference between the two groups in terms of age, parity and menopausal status.

Table 2 demonstrates the technical characteristics of both groups. There was an average of 3.48 mm difference in the initial cervical dilatation prior to hysteroscopy between the Evening Primrose Oil group and placebo group. This was clinically significant. All patients in the placebo group required cervical dilatation prior to hysteroscopy and it took an average of 53.56 seconds to dilate the cervix to Hegar size 10 in the placebo group compared to 17.43 seconds in the Evening Primrose Oil group. All of the nulliparous women in the Evening Primrose Oil group (6 patients) and the placebo group (3 patients) required cervical dilatation. In these patients, the largest initial cervical dilatation observed in the Evening Primrose Oil group was 7mm and only 4 mm in the placebo group. Two patients in the Evening Primrose

Table 1. Demographic and clinical characteristics of the patients according to treatment groups.

Characteristics	Primrose Oil Group (n=24)	Placebo Group (n=18)
Age, in years		
Mean (SD)	40.33 (8.07)	41.94 (9.52)
Min-Max	29-56	27-59
Parity, n (%)		
Nullipara	6 (25.00)	3 (16.67)
Primipara	6 (25.00)	4 (22.22)
Multipara	12 (50.00)	11 (61.11)
Indication for Hysteroscopy, n (%)		
Endometrial polyp	18 (75.00)	10 (55.56)
Submucous myoma	5 (20.83)	7 (38.89)
Thickened endometrium	1 (4.17)	1 (5.56)
Hysteroscopic Procedures, n (%)		
Polypectomy	18 (75.00)	7 (38.89)
Myomectomy	4 (16.67)	6 (33.33)
Targeted endometrial biopsy	2 (8.33)	5 (27.78)
Menopause	5 (20.83)	6 (33.33)

Oil group were nulliparous postmenopausal women. Both had initial cervical dilatation of 3mm. One patient in the placebo group was nulliparous postmenopausal with initial cervical dilatation of 3mm.

Of the 24 patients in the Evening Primrose Oil group, only 2 were given inhalational general anesthesia while the rest were given spinal anesthesia. All patients in the placebo group were given spinal anesthesia.

At the end of the procedure, only 4 surgeons agreed that there was subjective ease in cervical dilatation in patients assigned to the Evening Primrose Oil group. None of the surgeons thought that cervical dilatation was easy in any of the patients in the placebo group.

Visual analog scale (VAS) for pain was used to assess postoperative pain. Only mild pain (VAS of 1-3) was reported for both groups.

Two (2) patients in the Evening Primrose Oil group had softening of stools one day after the procedure. Only supportive management in the form of intravenous fluids was administered. There were no reported adverse events in the placebo group.

Table 3. Comparison of the two groups with respect to postoperative pain.

Postoperative Pain (VAS)	Primrose Oil Group (N=21)	Placebo Group (N=18)
0	13 (61.90)	5 (27.78)
1	4 (19.05)	5 (27.78)
2	4 (19.05)	6 (33.33)
3	0	2 (11.11)

Table 2. Technical characteristics of the patients according to treatment groups.

Characteristics	Primrose Oil Group (N=21)	Placebo Group (N=18)	Difference [95% Confidence Interval]
Initial cervical dilatation prior to hysteroscopy(mm)			
Mean (SD)	7.81 (2.29)	4.33 (1.33)	3.48 [2.23 to 4.72]*
Min-Max	2-10	2-7	
Patients requiring cervical dilatation, n (%)	10 (47.62)	18 (100.00)	-52.38% [-31.02% to -73.74%]***
Subjective ease of cervical dilatation			
<10 strongly disagree	0	0	
10-15 disagree	2 (9.52)	10 (55.56)	
16-20 neither agree or disagree	15 (71.43)	8 (44.44)	
21-25 agree	4 (19.05)	0	
Duration of cervical dilatation (seconds)			
Mean (SD)	17.43 (20.34)	53.56 (17.17)	-36.13 [-48.46 to -23.80]*
Min-Max	0-52	31-102	

Independent t-test P-value=0.0000* ; P-value=0.0001**; Fisher's Exact P-value = 0.000

Table 4. Adverse events in the evening primrose oil group.

Pt No	Nature	Severity	Seriousness	Intervention	Relationship to Study Intervention	Outcome
10	Softening of stools	Mild	No	Supportive [IV fluids]	Yes	Resolved on day 2 postop
28	Softening of stools	Mild	No	Supportive [IV fluids]	Yes	Resolved on day 2 postop

One patient in the Evening Primrose Oil group and 1 patient in the placebo group had cervical tear. Another patient in the placebo group had creation of false tract. All these patients were observed postoperatively and were discharged asymptomatic.

Discussion

Hysteroscopy is an important tool in the diagnosis and management of intrauterine lesions. Over the past decades, advances in endoscopic surgical instrumentation have made operative hysteroscopy the therapeutic procedure of choice in patients with intrauterine abnormalities[1]. The common complications encountered during operative hysteroscopy include fluid overload, uterine perforation, bleeding, infection, cervical tears and creation of false tracts.[2] Difficulty in cervical dilatation is associated with almost 50 percent of complications encountered during hysteroscopy.[3] Cervical priming before hysteroscopy reduces the need for cervical dilatation, facilitates the hysteroscopic procedure and minimizes cervical complications.

In other countries, misoprostol is the recommended drug of choice for cervical priming prior to operative hysteroscopy due to its easy application, reduced cost and patient convenience.[1] However, in the Philippines, misoprostol has been cited as an abortive drug and cannot be used for obstetric and gynecologic indications. On the other hand, laminaria tents are not readily available and are costly. This study was undertaken to evaluate the use of Evening Primrose Oil as an alternative cervical priming agent in gynecologic procedures. It is already gaining popularity as a cervical priming agent for vaginal delivery.[11] It is readily available and affordable with no known toxic or severe side effects.

Similar to trials of Evening Primrose Oil in pregnant patients, this study proved that it can be used as a cervical priming agent prior to gynecologic procedures. The difference in baseline cervical dilatation was used as the main outcome indicator of the success of Evening Primrose Oil in adequately preparing the cervix prior to hysteroscopy.

Side effects associated with Evening Primrose Oil include nausea, softening of the stools and headache. Toxic side effects are rare and doses as high as 8 grams daily are well-tolerated by most patients. Only 2 patients in the study group developed adverse reaction in the form of mild softening of stools that was resolved spontaneously. Preparation of the drug may contain sugar and so diabetics are cautioned in taking this medication. In addition, Evening Primrose Oil may lower seizure threshold and increase anticonvulsant dosage requirements.

The incidence of complications in both groups were quite low. This could be attributed to the experience of the surgeons and adequate anesthesia that might have relaxed the cervix. Infertility was not a factor in cervical dilatation in both groups. Variables that might have affected the results are nulliparity, type of anesthesia used and menopausal status of the patients. Difficulty in entering the internal cervical os is encountered more commonly in nulliparous and menopausal women. To get a beneficial effect of Evening Primrose Oil on cervical ripening, estrogenic activity might be necessary and when pretreated with local estrogen, Evening Primrose Oil might ameliorate cervical priming in postmenopausal and nulliparous women. There was no significant effect of the type of anesthesia used on the cervical dilatation since most patients were given spinal anesthesia. However, this should be explored further since most studies in foreign countries indicate that intravenous general anesthesia in the form of propofol is the safest and most popular method used in hysteroscopy. Choice of anesthesia depends on several factors including the procedure, the facility, the surgeon's experience and preference, the hysteroscopy equipment and patient factors. Spinal and general anesthesia can be equally effective, although general anesthesia produces a dose-dependent reduction in uterine tone. Spinal anesthesia is associated with increased recovery time due to prolonged motor or sensory block.

Considering all these, the results of this trial should be interpreted with caution because more studies are needed to evaluate the beneficial effects of Evening Primrose Oil as a cervical ripening agent before it can be used for such purpose in gynecologic procedures.

Conclusion

A randomized, double-blind, placebo-controlled trial was performed to determine the efficacy of Evening Primrose Oil as a cervical ripening agent when used prior to operative hysteroscopy. A total of 42 patients were included in the study, 24 in the Evening Primrose Oil group and 18 in the placebo group. The primary outcome was initial cervical dilatation prior to hysteroscopy. The number of patients requiring cervical dilatation and duration of cervical dilatation to Hegar dilator size 10 were included as secondary outcomes.

Recommendation

Further studies are required to define the optimal dose and timing of Evening Primrose Oil as a cervical priming agent prior to hysteroscopy. Also, its relevance in nulliparous and menopausal patients in whom maximal difficulty in dilating the cervix is encountered should be considered.

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