The efficacy of evening primrose oil as a cervical ripening agent for gynecologic procedures: A single-blinded, randomized controlled trial*

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ABSTRACT

Background: Evening Primrose Oil (EPO) is one of the most commonly prescribed cervical ripening agents. Cervical ripening is the softening, effacement, and dilation of the cervix that occur prior to active labor, and is an intervention that is used for certain indications, such as postdates pregnancy. There are gynecologic cases wherein the cervix is closed and dilatation has not occurred making the procedure difficult. In studies, EPO works by softening and ripening the cervix in the pregnant woman. More likely it has the same effects in a non-pregnant patient with regards to softening and dilating the cervix during gynecologic procedures.

Methods: The study was conducted in a tertiary hospital. Patients scheduled for gynecologic procedures were randomly grouped under the control and study group. Both groups had an internal examination during admission. The study group, in addition, were given EPO 4 capsules intra-vaginally, 6 hours prior to the contemplated procedure. Cervical characteristics were assessed initially on admission and pre-proedure. Consistency were assessed using the Consistency Index (CI) and graded as firm=1, medium=2 and soft=3 . Dilatation were assessed using the Dilatation Index (DI) and graded as closed=1, admits tip =2 , >1cm= 3. Pre-procedure, cervical characteristics and the CDI of both groups were assessed. Hegars dilators were used to assess the degree of dilatation, noting the diameter of dilator that can be introduced freely, and to what diameter the cervix can be maximally dilated.

Results: 80 patients were enrolled in the study; 39 patients were assigned in the control group and 38 patients were assigned in the study group (3 were excluded). In the study group, their DI improved by 36.2% (pre = 1.53+/-0.51 to post = 2.08+/-0.49) (p<0.001), CI increased by 115.9% (pre=1.16+/-0.37 to post = 2.50+/-0.65) (p<0.001), and their CDI changed by 70.6% (pre=2.68+/-0.74 to post = 4.58+/-0.95) (p<0.001). The changes of scores in all the cervical parameters in the study group were statistically significant.

Conclusion: EPO 4 capsules punctured and administered intra-vaginally 6 hours prior to contemplated gynecologic procedure can promote cervical ripening as exhibited by the improvement of the CDI from initial assessment to pre-procedure assessment.
Keywords: Evening Primrose Oil, EPO, Cervical Ripening Agents

INTRODUCTION

Evening primrose oil (EPO) is one of the most commonly prescribed non-pharmacologic cervical ripening agent used in the United States. Cervical ripening, defined as the softening, effacement, and dilation of the cervix that occur prior to active labor, is an intervention used for certain indications such as postdates pregnancy.[1] Currently, multiple options exist for cervical ripening ranging from natural and herbal methods to more invasive medicines or procedures, such as prostaglandin preparations, membrane stripping, amniotomy, or mechanical means by laminaria and Foley catheter balloon.[1-3] In local settings, EPO has been used by some clinicians to ripen the cervix in patients prior to a gynecologic procedure. There are gynecologic cases wherein the cervix is closed and dilatation has not occurred making the procedure difficult. In studies, EPO works by softening and ripening the cervix in pregnant women.[1-2] More likely it has the same effects in a non-pregnant patient with regards to softening and dilating the cervix during vaginal gynecologic procedures.

Review of Related Literature:

Evening primrose is a biennial herb that grows wild in parts of North America and Europe. Oil extracted from the seeds of the evening primrose contains linolenic acid, gamma linolenic acid, and vitamin E. Gamma linolenic acid is a known precursor of prostaglandin E and several other active substances, and is said to be the constituent of the oil responsible for its therapeutic effects. The mature seeds contain approximately 7-10% gamma-linolenic acid and 70% linoleic acid.[1]

Although its efficacy has been studied in the relief of symptoms of a number of medical conditions, its use has not been well studied, if at all, for the purpose of cervical ripening.[2] Prostaglandins soften the cervix so that it is ripe to begin dilation and effacement as labor progresses. The marked changes within the extracellular matrix during cervical ripening during parturition are accompanied by stromal invasion with inflammatory cells.[3] This has led to a model in which cervical ripening is considered an inflammatory process such that cervical chemo-attractants attract inflammatory cells, which in turn release proteases that may aid degradation of collagen and other matrix components. EPO contains linoleic and gamma-linolenic acid which are metabolized into arachidonic acid. A possible fate of arachidonic acid is to be transformed into a group of metabolites called eicosanoids (ex. prostaglandin, thromboxane, leukotriennes). Eicosanoids produced from arachidonic acid tend to be pro-inflammatory.

Controlled clinical trials have been conducted for the use of evening primrose oil for a variety of disorders, including atopic dermatitis, rheumatoid arthritis, diabetic neuropathy, multiple sclerosis, many cancers, Raynaud's phenomenon, ulcerative colitis, preeclampsia, premenstrual syndrome, menopausal flushing, breast cysts, mastalgia, Sjogren's syndrome, schizophrenia, and hyperactivity.

Evening Primrose Oil capsules have been used by pregnant

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woman orally in an effort to aid in cervical ripening, however this does not seem to shorten the length of pregnancy or labor. Some women also report inserting Evening Primrose Oil capsules vaginally during the third trimester of pregnancy, to assist cervical ripening.[1-2] More or less, in the same manner cervical ripening starts in pregnancy, EPO is likely to initiate an inflammatory response thus promoting cervical ripening in non-pregnant patients.[2-3]

SIGNIFICANCE OF THE STUDY

Evening Primrose Oil has been to some extent effective in ripening the cervix in term pregnant patients. The cervices, of some gynecologic patients, are unfavorable and closed during the procedure thus resulting to a prolonged operating time, more discomfort to the patient, and much worse, a failed procedure. Preoperative usage of EPO in gynecologic patients may probably aid in ripening and dilating the cervix as with pregnant patients.

OBJECTIVES

General Objectives:
To determine the effect of intra-vaginally applied EPO on the cervix of patients undergoing gynecologic procedures.

Specific Objectives:
1. To determine the demographic profile of patients in:
    a. Control group (non-EPO)
    b. Study group (with EPO)
2. To determine and compare the cervical findings of the control and study group during initial assessment and prior to the gynecologic procedure:
    a. Dilatation
    b. Consistency
3. To determine and compare the dilatation status of the control and experimental group using Hegars dilator.

METHODS

Study Design:
Single Blinded, Randomized Controlled Trial

Study Setting & Data Collection:
The study was conducted at a tertiary hospital from February 2013 to April 2014. Patients scheduled for gynecologic procedures were assigned under the control and study group randomly. Both groups had an initial internal examination done by one of only two residents assigned to assist in this study. A pre-study assessment between the two admitting residents was done to ensure that they have similar grading with cervical characteristics.

The study group was given four (4) punctured capsules of EPO intra-vaginally, six hours prior to the contemplated procedure while the control group received no intervention. During initial assessment, their cervices were assessed in terms of consistency and dilatation. Consistency was assessed using the Consistency Index (CI) and graded as firm=1 (like the tip of the nose), medium=2 (like the earlobe) and soft=3 (like the lip). Dilatation was assessed using the Dilatation Index (DI) and graded as closed=1, admits tip (less than 1 cm) =2 , ≥ 1cm= 3.

Immediately prior to the gynecologic procedure, after induction of anesthesia and patient preparation, an internal examination was done by the researcher to assess cervical characteristics and the CI/DI of both groups. A Hegars dilator was also used by the researcher to assess the degree of dilatation, noting up to what diameter of dilator can be introduced freely, and to what diameter the cervix can be maximally dilated. These data were recorded in the assessment sheets.

A total of 80 patients were explained of the intervention, consented to and were subsequently enrolled in the study. Patients were randomly assigned to each study arm. Randomization was done using a random number generator. Even numbers were assigned to the study group, odd numbers were assigned to the control group. One patient from the control group was excluded due to inadequate recording of cervical findings prior to the procedure. Two patients from the study group were excluded since they did not meet the allotted time of EPO exposure. The control group had 39 patients whereas the study group had 38 patients.

Inclusion Criteria:
1. Patients undergoing gynecologic procedures such as Dilatation and Curettage, Diagnostic & Operative Hysteroscopy, Endometrial Biopsy.
2. All gynecologic service patients and patients who had consent from their private physicians were enrolled in the study.

Exclusion Criteria:
1. Pregnant patients.
2. Gynecologic procedures done for miscarriages.
3. Patients whose cervices were ≥ 1 cm. dilated on initial assessment.

Sample Size:
A sample size of 38 patients in the study group and 39 patients in the control group achieved a 90% study power.

Data Analysis:
Data was analyzed using mean, frequency, standard deviation and percentage distribution. Unpaired T-testing was used to compare the mean between the two groups. Z-test of Difference in Proportions was used to analyze the difference in percentage.

Definition of Terms:
Gynecologic Procedures: includes Dilatation and Curettage, Diagnostic & Operative Hysteroscopy, Endometrial Biopsy
EPO: Evening Primrose Oil
Consistency/Dilatation Index (CI/DI/CDI): grading system for cervical characteristic assessment used in the study for uniformity of cervical assessment (See Appendix 1)

RESULTS

Table 1 reflects the baseline characteristics of the patients in both groups. In the control group had a total of 39 subjects with a mean age of 43.64+/-9.67. Eleven were nulliparous (28.2%) while were multiparous (59%). Twenty-four patients had normal spontaneous delivery as the previous delivery (61.5%) and 6 patients were menopausal (15.4%).

The patients in the study group had a mean age of 42.45+/-0.28. Eleven were nulliparous (29%) and 20 were multiparous(53%). Nineteen patients had normal spontaneous delivery as the previous delivery (50%), and eight patients were menopausal (21%).

Analysis showed that the differences in the patients' age, parity, previous delivery and hormonal status were not statistically significant between the control and study group ($p>0.05\alpha$).

Table 2 shows the procedure profiles of both groups. The common procedure in the control group was Dilatation and Curettage (82.5%). A similar profile was also noted with the study group (83.2%). As for analgesia, majority in the study group (70.2%) and control group (68.2%) had Total Intra-venous Analgesia.

Table 1: Baseline Characteristics

Mode of Treatment Total No. of Cases	Non-EPO 39		EPO 38		P-VALUE
Baseline Characteristics					
Marital Status					
married	30	76.9%	33	87%	0.259
single	9	23.1%	5	13%	0.259
Age (years)					
Mean	43.64		42.45		0.601
Std. Deviation	9.67		10.28		
Parity					
nulli (G0P0)	11	28.2%	11	29%	0.943
multi (G2-G3)	23	59.0%	20	53%	0.575
grand multi G4 and above	5	12.8%	7	18%	0.498
Delivery Status					0.308
NSVD	24	61.5%	19	50%	0.571
Complete abortion	2	5.1%	1	3%	0.308
Incomplete abortion	0	0.0%	1	3%	
CS					
once	3	7.7%	5	13%	0.432
twice	0	0.0%	1	3%	0.308
thrice	0	0.0%	1	3%	0.308
None	36	92.3%	31	82%	0.161
Menopause	6	15.4%	8	21%	0.519

Table 2: Patients' Procedure Profiles

Mode of Treatment Total No. of Cases	Non-EPO 39		EPO 38		P-VALUE
Procedure					
D&C	33	82.5 %	32	83.2 %	0.961
Diagnostic/Operative Hysteroscopy	4	11.2 %	3	8.3 %	0.974
Endometrial BX	2	6.3 %	3	8.4%	0.073
Analgesia					
CSEA	1	2.6%	0	0.0%	0.320
GA	4	10.5 %	0	0.0%	0.022
Oral	2	5.9 %	3	8.5%	0.073
SAB	5	12.8%	8	21.3 %	0.335
TIVA	27	68.2%	27	70.2%	0.861
Operative Time					
Overall					
Mean	15.62		13.53		0.321
Std. Deviation	7.82		10.39		
All D&C group	*n=33*		*n=32*		
Mean	14.33		11.28		0.043
Std. Deviation	6.89		4.87		

Moreover, as for their overall operative time, the control group had a slightly higher average of operative duration (15.62+/7.82) as compared with the study group (13.53+/-10.39) (p=0.321). Shorter operative time was noted for dilatation and curettage procedures in the study group (11.28+/-4.87) as compared with the control group (14.33+/-6.89) (p=0.043).

Table 3 shows the Cervical Characteristics of the Control group. Analysis showed that during the initial cervical assessment of patients, with regards to dilatation, 25 cases had a cervix that admitted the tip of the finger ("admits tip") while 14 cases had a closed cervix. During pre-procedure assessment, 92% with "admits tip" cervix remained as such while 8% became 1cm dilated. On the other hand, those who had a closed cervix, 85.71% remained closed while 14% became "admits tip". Twenty-three cervices were firm on initial assessment. Twenty-two cervices (96%) still remained firm and 1 patient (4%) had medium consistency prior to the procedure.

Table 4 shows the Cervical Characteristics of the Study Group. Out of the 20 cervices that admitted the tip of the finger on initial assessment, nineteen patients (95%) remained the same during pre-procedure assessment. Among the 18 patients with closed cervix on initial assessment, fifteen patients (83%) had an "admits tip" cervix pre-procedure. Furthermore, of the 31 patients who came in with a firm cervix, 2 patients (6%) retained its firmness, 11 patients (35%) progressed to medium and eighteen patients (58.1%) had a soft cervix 6 hours after EPO exposure. And of the 7 patients with medium consistency of cervix on initial assessment, five patients (71.4%) became soft prior to the procedure as well.

The comparison of Consistency/Dilatation Index in both groups is shown in Table 5. In the control group, changes in the cervical characteristics were as follows: DI increased by 6.2% (pre mean=1.64+/-0.49 to post mean=1.74+/-0.50) (p=0.074), CI increased by 1.9% (pre=1.36+/-0.49 to post=1.38+/-0.49) (p=0.324), and CDI increased by 4.3% (pre = 3.00+/-0.79 to post = 3.13+/-0.83) (p=0.083). As noted, their DI and CDI did improve but were not statistically significant.

On the other hand, in the study group, the DI improved by 36.2% (pre=1.53+/-0.51 to post=2.08+/-0.49) (p<0.001), CI increased by 115.9% (pre=1.16+/-0.37 to post=2.50+/-0.65) (p<0.001), and their CDI changed by 70.6% (pre=2.68+/-0.74 to post = 4.58+/-0.95) (p<0.001). The changes of scores in all the cervical parameters among those with EPO were statistically significant.

Lastly, as noted in Table 6, with Hegars dilator, average score in the study group were statistically higher as compared with the control group. In the study group, Hegars dilator freely admitted started with a wider diameter as compared with the control group (4.21+/-1.44 vs 2.51+/-1.12) and maximum dilatation were higher in the study group as well (9.21+/-1.53 vs 5.77+/-1.98) (p<0.001).

DISCUSSION

A local study by Ty-Torredes in 2004 employed EPO as cervical ripening agent in term gravids and concluded that EPO taken orally has ripening effects measured in Bishop Score and cervical length changes.[5] Another local study by Cerna in 2010 determined the effect of oral EPO on the cervical length of term gravids and yielded similar results.[6] This present study on the other hand, enrolled gynecologic patients as study subjects. In previous studies, the mechanism of promoting cervical ripening is the same in either a pregnant or non-pregnant cervix which involves an inflammatory mechanism.[7]

Sawai and O'Brien in 1995 documented the use of exogenously applied prostaglandin agonists that will induce cervical ripening in term gravids.[7] This study employed EPO exogenously applied over the cervix of a gynecologic patient in hopes to ripen the cervix and have easier dilatation of the cervix to gain access to the cavity and have a successful procedure.

Similar with the study by Capco and Tanangonan, EPO was also used in this study intra-vaginally to achieve cervical ripening effects prior to a gynecologic procedure.

The demographic distribution of this study showed no significant statistical difference between both groups. The cervical status change noted in the control group, although not statistically significant, may be attributed to the subjective difference in assessment among the examiners (admitting resident and researcher). Thus, the Consistency and Dilatation Index was made to limit the inter-observer difference and as much as possible, have uniformity in the reporting of cervical findings.

A study by Capco and Tanangonan in 2009 noted the cervical priming effects of EPO in patients prior to hysteroscopy. They noted that patients under the study group had a wider diameter of cervical dilatation using Hegars dilator after EPO exposure and the placebo group required longer duration of dilatation.[8]

This study showed firm cervices were noted to be either medium or mostly soft in consistency 6 hours after exposure to EPO. Although there was less improvement with the dilatation status after exposure, there was further dilation when Hegars dilators were used. There is no effect with dilatation mainly because there is nothing presenting at the internal os to provide pressure and cause dilation as opposed to a cervix during labor. The Consistency/ Dilatation Index (CDI) were higher in the study group which means they have better consistencies and dilatation status after exposure to EPO. The changes of scores in all the cervical parameters in the study group as compared with the control group were statistically significant.

Using the Hegars Dilator, the mean admitting Hegars with the study group was 4 cm as compared with the control group was 2 cm. Maximal dilatation rates were higher with the study group. Degradation of the collagen cross-linkages could explain the ease of dilating these cervices which was noted to occur in the study group. We have observed that the procedure duration for all dilatation and curretage in the study group were shorter as compared to the control group. This could probably be attributed by the faster access to the uterus due to a favorable cervix.

CONCLUSION

EPO 4 capsules punctured and administered intra-vaginally 6 hours prior to contemplated gynecologic procedure can promote cervical ripening as exhibited by the improvement of the CDI from initial assessment to pre-procedure assessment. Moreover, a significant difference between the CDI in the study group and the control group was noted. Those patients in the study group have favorable cervices that can be easily dilated with the aid of Hegars dilator to facilitate entry of instruments to complete the procedure. There were no untoward or serious side effects noted after vaginal administration of EPO.

RECOMMENDATIONS

For a more accurate assessment and minimize the inter-observer difference of the cervical changes that occurs among the groups, the researcher suggests to make use of graded dilators during initial assessment. We did not make use of this approach in this study because of the discomfort on the patients' behalf. As far as cervical changes are concerned, there is an effect when 4 capsules were used. A study which will make use of a lower dosage would be beneficial for the patients.

Table 3: Cervical Characteristics of the Control Group

Main Clinical Parameters	No. of Pre-operative Cases	Pre-procedure Outcomes					
Dilatation		**1 cm**		**admits tip**			**closed**
admits tip	25	2^{ns}	8%	23	92%	0	0.00%
Closed	14	0	0%	2^{ns}	14%	12	85.71%
Consistency		**Firm**		**med**			
Firm	23	22	96%	1^{ns}	4%		
Med	16	0	0%	16	100%		

Note: (*) means statistically significant at 0.05alpha, ns mean not statistically significant p>0.05 alpha

Table 4: Cervical Characteristics of the Study Group

Main Clinical Parameters	No. of Pre-operative Cases	Pre-procedure Outcomes					
Dilatation		**1 cm**		**admits tip**		**closed**	
admits tip	20	1^{ns}	5%	19	95%	0	0.00%
Closed	18	0	0%	15	83%	3^{ns}	16.7%
Consistency		**Firm**		**med**		**soft**	
Firm	31	2	6%	11*	35%	18*	58.1%
Med	7	0	0%	2	29%	5^{ns}	71.4%

Note: (*) means statistically significant at 0.05alpha, ns mean not statistically significant p>0.05alpha

Table 5: Comparison of Consistency/Dilatation Index

Cervix Characteristics Scoring	Non-EPO		EPO	
	MEAN	SD	MEAN	SD
DI				
pre	1.64	0.49	1.53	0.51
post	1.74	0.50	2.08	0.49
difference	-0.10	0.31	-0.55	0.60
% change	↑6.2%		↑36.2%	
p-value	0.074		<0.001	
CI				
pre	1.36	0.49	1.16	0.37
post	1.38	0.49	2.50	0.65
difference	-0.03	0.16	-1.34	0.71
% change	↑1.9%		↑115.9%	
p-value	0.324		<0.001	
CDI				
pre	3.00	0.79	2.68	0.74
post	3.13	0.83	4.58	0.95
difference	-0.13	0.34	-1.89	1.16
% change	↑4.3%		↑70.6%	
p-value	0.083		<0.001	

Table 6: Comparison of Hegars Dilation Characteristic

HEGARS' SCORES Total No. of Cases	Non-EPO 39	EPO 38	P-VALUE
On Admission			
Mean	2.51	4.21	<0.001
Std. Deviation	1.12	1.44	
Maximum			
Mean	5.77	9.21	<0.001
Std. Deviation	1.98	1.53	

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