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Cervical Ripening Before Hysteroscopy In Infertile Patients: A Randomized, Double-Blind, Placebo-Controlled Comparison Of Sublingual And Vaginal Misoprostol

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Abstract: Objective: *To compare the effects of 400 µg Misoprostol administered through vaginal and sublingual route for preoperative cervical ripening in infertile patients prior to hysteroscopy and to study the side effects and complications.*
Methods: *This hospital based prospective double-blind study was conducted on 88 infertile patients posted for hysteroscopy. A pre-treatment Hegar's dilator test was done and findings noted for all patients. Randomization of patients was done by flip of coin method for administration of 400 µg Misoprostol sublingually or vaginally 8-12 hours prior to surgery. The primary outcome in this study was the postoperative cervical width as measured by the largest number of Hegar dilator that could be inserted without resistance. The side effects and complications during surgery for each group were also noted.*
Results: *Patients were randomized to receive sublingual (n = 44) and vaginal (n = 44) Misoprostol. The groups were comparable in terms of age, parity, rural/urban , history of vaginal delivery and surgeon type. The preoperative cervical width in the sublingual group : 0.34 ± 0.67mm and vaginal group: 0.29 ± 0.54 mm was statistically similar among both groups. The post-operative cervical width in the sublingual group was 6.45 ± 1.19 and vaginal group was 8.27 ± 1.11.The difference between the two groups was found to be statistically significant(p value<0.01) though the side effects and complications during the hysteroscopy were comparable.*
Conclusion: *The outcome of cervical ripening with Misoprostol prior to hysteroscopy in young infertility patients by the sublingual and vaginal routes, vaginal administration is more effective than sublingual route.*
Keywords: *Cervical ripening, Hegar's dilator, Misoprostol*

I. Introduction

Hysteroscopy is a valuable diagnostic and therapeutic modality in management of infertility. It is utilized for diagnostic and operative intervention for endometrial polyps, sub mucous and pedunculated myomas, intrauterine adhesions and uterine septa. It is also useful for the diagnosis of congenital anomalies and evaluating endocervical anatomy[1].

Hysteroscopy requires insertion of the hysteroscope through the cervical canal, which necessitates cervical dilatation at up to Hegar dialator No.8-10 as the diameter of the outer sheath of the hysteroscope range in size from 7-10 mm (average 8 mm) in diameter[2]. Though nowadays with the upcoming of office hysteroscopes of narrower diameter, the need of preoperative cervical dilatation is not necessary, the institute where the present study has been conducted hysteroscopes of wider diameter are still in vogue because of its sturdier design and its capability to cater to large number of patients.

The positioning a hysteroscope in the uterine cavity solely for diagnostic purpose is largely limited due to potential risk of cervical trauma and uterine perforation. Other adverse events such as infection, excessive bleeding and complications related to the distension media are extremely uncommon (0-1%) .Almost half of the complications of operative hysteroscopy occur during cervical entry.

These include: - Cervical tear , Creation of false passage , Uterine perforation ,Subsequent cervical stenosis and incompetence.[3]

Because of these complications, medical means of softening or dilating the cervix, known as ripening, has become an integral part of pre-operative care. Different cervical ripening agents are now being used prior to the procedure. In the past, laminaria and prostaglandins of E series have been used effectively in dilating and softening of the cervix [4,5]. However laminaria may not be suitable in women who have marked cervical stenosis and PGs such as dinoprostone are expensive and require special storage condition.Misoprostol has now emerged the drug of choice as it is cheaper, highly efficacious, and stable at room temperature and is available as tablet

that can be used both sublingually and vaginally. (Ngai et al, 1997[6]; Preutthipan et al[7], 1999, 2000; Thomas et al[8], 2002). The efficacy of Misoprostol as a cervical ripening agent on pregnant uterus has been well established. However there are varying reports regarding efficacy and incidence of side-effects when Misoprostol is used prior to hysteroscopy in non pregnant patients. Also the consensus regarding the optimal dose and duration of administration is lacking. Few authors report favourable outcome with 200-400 mcg administered atleast 8-12 hours prior to operative hysteroscopy. However a similar dose administered 3-4 hours prior to the procedure has also found to have a favourable outcome.

The present study aims to assess and compare the efficacy and safety of 400 µg Misoprostol administered either by sublingually v/s vaginal route as a cervical priming agent 8-12 hours prior to hysteroscopy.

II. Method

The study was conducted at Department of Obstetrics and Gynaecology at Mahila Chikitsalaya, Jaipur from April 2012 to September 2013. This study is a prospective randomized double-blind clinical trial with patients allocated to either oral or vaginal Misoprostol by flip a coin method.

88 infertile patients posted for hysteroscopy was recruited in the present study. Written informed consent by each subject was taken before the study. Clinical history was obtained and physical examination of all subjects done.

Each participant underwent a vaginal speculum examination and cervical diameter measured with a Hegar's dilators in outpatient clinic without any anaesthesia prior to administration of Misoprostol. The diameter of the cervical canal was assessed by placing decreasing sized Hegar dilators with minimal pressure through the cervical canal to a distance of 3 cm starting with Hegar dilator No. 10. The largest Hegar's dilator that could be inserted without resistance was considered to be the clinical diameter.If there was resistance even with Hegar dilator of 1mm i.e. no.1 then result was recorded as 0. Patients was randomly assigned (Flip of coin method) to the following regimens: -

The sublingual group - received 400 µg of Misoprostol orally and receive as placebo one vaginal tablet of Lactobacillus Acidophillus.

The vaginal group - received 400 µg of Misoprostol vaginally placed in posterior vaginal fornix and receive as placebo one oral tablet of commercially available Vit B6 (Niacin).

Surgery was performed the following morning 10-12 hrs after Misoprostol administration. To prevent bias, in all cases, the vagina was cleaned of any remnant of Misoprostol or Lactobacillus Acidophillus tablets before the patients were sent to operation room. Patients were asked about the possible side-effects of Misoprostol before induction of general anaesthesia such as abdominal pain, nausea, flatulence, headache, dyspepsia, vomiting and constipation.

The cervical diameter was re-evaluated immediately prior to beginning of hysteroscopy using the same technique but under general anaesthesia. At the time of entry, if the cervical canal was too small or tight precluding passing of the hysteroscope (diameter of outer sheath = 7 mm) then further dilatation was performed to Hegar No. 9.

The outcome measures in the study were pre and post treatment cervical width, the number and percentage of patients who required cervical dilatation to allow passage of hysteroscopy, complications during the procedure, back flow from the cervix complicating satisfactory uterine distension and treatment emergent side-effect .

III. Results

From April 2012 to September 2013, 88 eligible patients were recruited into the trial and randomized to receive sublingual or vaginal Misoprostol . The two groups were comparable in terms of age, BMI (body mass index), parity, gravidity and history of vaginal delivery. The pretreatment Hegar's dilator test in sublingual group showed that the mean cervical width was 0.34±0.67 mm in comparison to the vaginal group which was 0.29±0.54 mm .(Table No.2)The difference however was not statistically significant i.e it was comparable in both groups. The post treatment Hegar's dilator test showed that in the sublingual group ,the mean cervical width was 6.45±1.19 mm in comparison to the vaginal group which was 8.27±1.11 mm.(Table No.2)

The mean change in the cervical width post treatment with 400 mcg Misoprostol when given sublingually was 6.11±1.24 mm as compared to that given vaginally which was 7.98±0.99 mm.The difference was found to be statistically significant with p value<0.001.(Table No.2)

The ease of performing hysterocopy as percieved by the operating surgeon was found to easy in 90.91%(40) cases in the vaginal group as compared to only 40.91%(18) cases in the sublingual group.(Table No.3)

None of the group had any complication during the procedure.However 2 of subjects belonging to the vaginal group who did not require cervical dilatation, had fluid leakage from the cervix complicated suitable uterine distension during the procedure.

The side effects was found to be comparable in both groups.22.73%(10) cases of vaginal group had drug emergent side-effects as compared to 13.64%(6) cases in the sublingual group.The difference however was not significant with p value>0.05,d.f=1 and χ^2 =1.222.

The most common side-effect was found to be was fever seen in 9.09% (8) cases followed by diarrhoea in 5.68% (5) cases and bleeding in 3.41%(3) cases. Fever was mostly seen in the subjects who received Misoprostol sublingually.Diarrhoea and bleeding was found only in the vaginal group.(Table No.5)

IV. Discussion

The present study showed that during hysteroscopy in infertility patients,pre-operative cervical ripening via vaginally administered Misoprostol(400µg) was superior to the same dose of Misoprostol given sublingually in terms of post treatment cervical width , ease of cervical entry as well as the need for cervical dilatation to Hegar's dialator No.10.Complication however was not seen in either group.Side-effects were more common in the vaginal group however the difference was not significant.

Cervical ripening is required to prevent complications during the transcervical procedure (Schulz et al, 1983[9]; Grimes et al., 1984[10]).Previous studies have shown that Misoprostol was effective when compared with placebo for cervical ripening (Atay et al.1997[11], Ngai et al.2001[12], Preutthipan et al 2001[7], Thomas et al 2002[8], Barcaite et al 2005[13]). However, there were few studies that have compared the efficacy of Misoprostol given by oral or vaginal route prior to operative hysteroscopy with varying results.Cem Batukan et al (2007)[14] did comparative study with 400 µg Misoprostol given by oral and vaginal route ,the results showing vaginal route being more effective than oral route in terms of mean cervical width, time required for cervical dilatation ,duration of surgery and associated complications during the procedure.The side effects were however comparable in between the two groups. Another study conducted by Yoo-Young Lee et al (2010)[15]to compare the efficacy of 400 µg of Misoprostol, administered either orally or vaginally 6–8 h prior to surgery or 400 µg sublingually 2–4 h prior to surgery. The preoperative cervical width [sublingual: 7.5+2.0 mm (8, 3–10); oral: 7.5+1.9 mm (7, 4–10); vaginal: 7.6+2.4 mm (8, 1–10)] was statistically similar among the groups. The mean post-treatment cervical widths for the sublingual oral, and vaginal Misoprostol groups were 7.5+2.0 mm (8, 3–10), 7.5+1.9 mm (7, 4–10), and 7.6+2.4 mm (8, 1–10), respectively .These cervical widths were similar among the groups.

In addition to the route of administration, the optimal dose and time interval from medication to surgery remain to be determined. Based on recent studies, 400 mcg has been most widely used dose for oral (Ngai et al., 2001[12]; Thomas et al., 2002[8],Choksuchat et al.,2006[16], vaginal (Barcaite et al., 2005[13]; Uckuyu et al., 2008[17] ,Singh et al., 2009 [18]), and sublingual (Saav et al., 2007[19]) administrations with good results. In the above cited studies, the time interval varied from 4 to 24 h for the oral and vaginal routes. So the dose used in the present study is 400 mcg in both groups administered 12 hours prior to hysteroscopy.

The frequencies and types of side effects were comparable among the two groups, consistent with the findings of previous studies (Choksuchat et al., 2006[16]; Batukan et al., 2008[14]).

This study was performed in a double blind fashion without a control group, which could be a potential weakness. Because it has been proven there are more complications during procedures without cervical ripening compared with cases with cervical ripening (Schulz et al., 1983[9] ; Grimes et al., 1984[10] ;Healey et al,2006 [20]), there should be an ethical problem with a control group. From the results of previous studies that had a control group (Ngai et al., 1997[6]; Preutthipan 2001[7]; Uckuyu et al., 2008[17]), the average cervical widths after Misoprostol administration were between 6 and 7.3 mm, which was similar to our results.

V. Conclusion

In conclusion, the outcome with regard to cervical ripening with Misoprostol prior to hysteroscopy in young infertility patients by the sublingual and vaginal routes, vaginal administration is more effective than sublingual route. However more studies are required regarding the optimal time period and dosage of Misoprostol administration for cervical ripening prior to hysteroscopy.

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Tables

Mean ± Sd of Hegar Dilator Test pre & post according to mode of treatment of subjects

	Mean ± Sd (Hegar Dilator Test)		Mean Change ± Sd	P- value	Significance
	Pre	Post			
Pervaginal	0.29 ± 0.54	8.27 ± 1.11	7.98 ± 0.99	< .001	HS
Sublingual	0.34 ± 0.67	6.45 ± 1.19	6.11 ± 1.24	< .001	HS

Pervaginal v/s **Sublingual P < .001 HS**

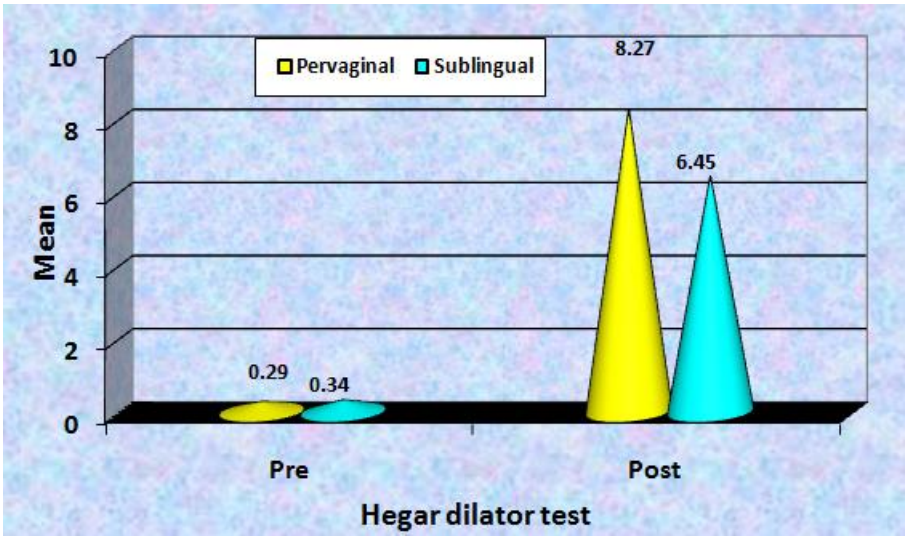

Table No.-2 Distribution according to surgery & mode of treatment of subjects

Surgery	Mode of treatment		Total
	Pervaginal	**Sublingual**	
Difficult	4 (9.09)	26 (59.09)	30 (34.09)
Easy	40 (90.91)	18 (40.91)	58 (65.91)
Total	44 (100.00)	44 (100.00)	88 (100.00)

$\chi^2 = 22.303$ d.f= 1 P < .001 HS

Table No.-3 Distribution according to side effect and mode of treatment of subjects

Side effect	Mode of treatment		Total
	Pervaginal	**Sublingual**	
Present	10 (22.73)	6 (13.64)	16 (18.18)
Absent	34 (77.27)	38 (86.36)	72 (81.82)
Total	44 (100.00)	44 (100.00)	88 (100.00)

$\chi^2 = 1.222$ d.f= 1 P > .05 NS

TABLE NO.4 Distribution according to side effect and mode of treatment of subjects

Side effect	Mode of treatment		Total
	Pervaginal	**Sublingual**	
Fever	2 (4.54)	6 (13.64)	8 (9.09)
Diarhoea	5 (11.36)	0 (0.00)	5 (5.68)
Bleeding	3 (6.82)	0 (0.00)	3 (3.41)
None	34 (77.27)	38 (86.36)	72 (81.82)
Total	44 (100.00)	44 (100.00)	88 (100.00)

Summary Of The Results

CHARACTERISTIC	MISOPROSTOL,200 Pervaginal(n=44)	Mcg doses Sublingual(n=44)	P value
Age(years)	28.05±4.06	28.0±3.44	>0.05
Nullipara	40(90.91)	35(79.55)	>0.05
Parous	4(9.09)	9(20.45)	>0.05
Rural	17(38.64)	7(15.91)	<0.05
Urban	27(61.36)	37(84.09)	<0.05
Pre-treatment cervical width(mm)mean±sd	0.29±0.54	0.34±0.67	<0.01
Post-treatment cervical width(mm)mean±sd	8.27±1.11	6.45±1.19	<0.01
Mean change±sd	7.98 ± 0.99	6.11 ± 1.24	<0.01
Ease of cervical entr	40(90.91)	18(40.91)	<0.01
Side effects	10(22.73)	6(13.64)	>0.05