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COMPARISON OFMISOPROSTOL 25µG WITH DINOPROSTONE0.5MG FOR CERVICAL RIPENING FOR INDUCTION OF LABOUR

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ABSTRACT
The purpose of the study was to compare the efficacy and safety or 25µg misoprostol vs Dinoprostone0.5mg for the cervical ripening of the cervix at term. Nullipara of para one women the unfavourable cervices after 37 completed weeks with live foetuses were randomised to receive either 25µg intravaginal misoprostol or 0.5mg intracervical dinoprostone. The doses were repeated after 6 hours if the bishop score was less than 5. In case the cervical ripening does not reached after two doses of ripening agents, oxytocin induction was at least 6 hours apart. Induction delievery interval, pregnancy outcome and neonatal outcome associated with use of drugs were compared. 100 women – 50 in each group were evaluated. Comparatively more women with misoprostol(52.4% vs 35.6%) achieved cervical ripening after the first dose. The mean Induction delievery interval was significantly shorter in the misoprostol group. In the misoprostol group 94.7% were delivered within 24 hours as compared to 70% in the dinoprostone group. No significant difference found in the intrapartum complications and fetal outcome. A 25µg dose of misoprostol is superior in promoting cervical ripening, being cost effectivedo not need any temperature conditionsand easy to administer, significantly shortened the insertion delievery interval. It is safe and effective for cervical ripening.

KEYWORDS: Tablet Misoprostol 25µg intravaginal, Dinoprostone gel 0.5mg intracervical, Cervical ripening, And Labour induction.

INTRODUCTION
Labour begins naturally for most women, but in approximately 5% of the pregnancies the cervix does not ripen normally and 10% to 11% of pregnancies, labour must be induced for medical or obstetric reasons.[1] Induction of labour in patients with an unfavorable cervix may result in prolonged, tedious labour and eventually increases operative deliveries. A failed induction in the presence of an unfavorable cervix is found in approximately 15% of the cases.

Cervical ripening refers to the softening of the cervix that typically begins prior to the onset of labor contractions and is necessary for cervical dilation and the passage of the fetus. Cervical ripening results from a series of complex biochemical processes that ends with rearrangement and realignment of the collagen molecules.

A recent study examining over 5,600 nulliparous women undergoing induction of labor found that a simplified Bishop score, including only cervical dilation, effacement and station, was equally as predictive as the traditional Bishop score in predicting vaginal delivery.

The most commonly used methodology to evaluate cervical ripening is the Bishop score because it is simple and has the most predictive value. This score uses cervical dilation, effacement, consistency, position and the station of the presenting part. In the 1960s Dr. Edward Bishop developed a pelvic scoring system using cervical dilatation, effacement, station, consistency and position with a possible range from 0-13.[2] Based on clinical experience, he concluded that elective induction in multiparous women with uncomplicated pregnancies at term was successful with a sore of > 8.

The total score is achieved by assessing the following five components on vaginal examination:
- Cervical dilation
- Cervical effacement
- Cervical consistency
- Cervical position
- Fetal station

The Bishop score grades patients who would be most likely to achieve a successful induction. The duration of labor is inversely correlated with the Bishop score; a score that exceeds 8 describes ' the patient most likely to achieve a successfulvaginal birth. Bishop scores of less than 6 usually require that a cervical ripening method be used before other methods.

They can be remembered with the mnemonic: Call PEDS For Parturition = Cervical Position, Effacement, Dilatation, Softness; Fetal Station.

SCORING

Each component is given a score of 0 to 2 or 0 to 3. The highest possible score is 13.

INTERPRETATION

A score of 5 or less suggests that labour is unlikely to start without induction. A score of 9 or moreindicates that labour will most likely commence spontaneously.[3]

Various methods have been developed to induce cervical ripening ill the preparation of the cervix for labor and delivery which are Prostaglandin E2 Gel (intracervical), Pessaries or inserts, Prostaglandin El(intravaginal), Oxytocin, Foley's Balloon Catheter (single or double), Low Dose Oxytocin, Antiprogesterone, Hygroscopic Dilators (laminaria tents, isapgol), Memberanes Stripping, Nitric Oxide Donors, Relaxin and breast stimulators causing oxitocin release.[4]

Two metanalysis comparing randomised trial of vaginal misoprostol with dinoprostone found an increased rate of vaginal delivery within 24 hrs and similar caesarean rates in the misoprostol group and hence conclude that misoprostol is more effective ripening agent.[5,6]

MATERIALS AND METHODS

The present study was conducted at Bebe Nanaki Mother and Child Care Hospital, Govt. Medical College Amritsar, comparing 25 µg vaginal misoprostol with 0.5 mg intracervical dinoprostone during the period from Feb 2016 to Aug 2016. The study was approved by the local institute and ethical committee.

The study was carried on 100 eligible pregnant women with obstetrical or medical indication for labour induction with no contraindication to vaginal delivery. These were grouped as under:

Group A: Group A 50women will receive 25µg Misoprostol 2 doses 6 hours apart.

Group B: Group B 50 women will receive 25µg Dinoprostone 2 doses 6 hours apart.

The induction of labour will be'done with pitocin after 6 hours of the last dose. Enrollment will be carried out from the admission room, OPD and from the ward.

Before the drug instillation, written consent will be obtained from the woman herself. Detailed systemic and clinical examination will be done and initial Bishop Score will be established.

Method of Instillation of PGE_2 GEL

After retracting the posterior vaginal wall with Sim's speculum, cervix and vagina is cleared of any mucous and discharge. After holding the anterior lip of the cervix with sponge holding forceps, Cerviprime gel is instilled into the cervical canal with the help of prefilled syringe. The syringe is immediately removed and the patient is kept supine with foot end slightly raised for half an hour.

The patient is reassessed completely 6 hours after the instillation of PGE_2 gel and following parameters are noted in each case:

1. Foetal heart rate
2. Cervical dilatation
3. Descent of presenting part
4. Bishop's scoring

METHOD OF PUTTING OF MISOPROSTOL (25 µG) INTRAVAGINAL

25µg Misoprostol tablet is inserted into the posterior vaginal fornix. Then patients are advised to lie on the left lateral position for half an hour in both the study groups. Uterine contraction and foetal heart sound (FHS) are monitored regularly every 30 minutes. If the cervix ripens then induction of labour was done by the pitocin after six hours after the last dose of misoprostol (25µg) or dinoprostone (0.5mg)".

DISCUSSION

A total of 100 eligible term gravidas participated in the study. 50 were enrolled in the misoprostol group and 50 in the dinoprostone group randomly. The patients in both groups were comparable in all respects. No patient were excluded after enrolmen The mean gestational age was in the misoprostol group was 272.42 days and in the dinoprostone was 268.94 day. There was no statistical difference in the gestational age in the either groups (p= 0.391). The mean gestational age was shown in the Table 1.

Table 1: Gestational age

Gestational age	Group	
	Misoprostol (n=50)	Dinoprostone (n=50)
<40 weeks	32	36
40-42 weeks	18	14
Total	50	50

(p value = 0.391).

Success of induction was defined as the onset of true labour pains with a Bishop's score of >5. The rates of successful induction were similar in the two groups as shown in the Table 2 (p=0.372).

Table 2: Success of induction

Success of Induction	Groups	
	Misoprostol (n=50)	Dinoprostone (N=50)
Yes	42	45
No	08	05
Total	50	50

(p=0.372).

The mode of delivery are shown in Table 03. Majority of the patients delivered vaginally in both groups. There was no significant difference in the rates of normal or operative deliveries. (p = 0.629).

Table 3: Modes of Delivery

Modes of delivery	Group	
	Misoprostol (n=50)	Dinoprostone (n=50)
Normal Vaginal Delivery	38	40
Caesarean Delivery	12	10
Total	50	50

(P value = 0.629).

Significantly more no of patients achieve vaginal delievery within 24 hours in the misoprostol group as compared to the dinoprostone group. Of those delivering within 24 hours 94.7% belonged to the misoprostol group as compared to 70% in the dinoprostone group (p=0.0044).

Table 4: Induction to vaginal delivery interval

Induction –to- vaginal delivery interval	Group	
	Misoprostol (n=38)	Dinoprostone (n=40)
<12 hours	2	12
12-24 hours	36	28
Total	**38**	**40**

(excluding failed inductions and Caesarean deliveries) (p value = 0.0044).

Neonatal outcome is comparable in both groups as shown in table below:

Table: 5

Neonatal Outcome	Group				P value
	Misoprostol		Dinoprostone		
	Number	Percentage	Number	Percentage	
Birth weight (Kg)					0.786
<2.5 kg	08	16%	7	14%	
>2.5kg	42	84%	43	86%	
Mean	2.89	2.778			
1 min APGAR Score					0.490
<7	04	4%	03	3%	
5 min APGAR Score					
<7	01	1%	02	2%	
Need for resuscitation	04	08%	03	06%	
NICU admissions	01	02%	02	04%	

In the present study, low dose vaginal misoprostol (25 µg 6 hourly) is compared with the established and time tested regimen employing intracervical dinoprostone for cervical ripening and induction of labour. Since the use of misoprostol is largely off label for obstetric indications, an appropriate dosage regimen has remained elusive. Many arbitrary dosage schedules have been employed in research and hence, an honest companson has been difficult to achieve The present study had used the 25 µg misoprostol vaginally 6 hourly dose for

cervical ripening for induction of labour in keeping with the latest WHO and ACOG recommendations.[27,28] The regimen used for dinoprostone has also been recommended by the ACOG in its guidelines on labour induction.[28] The trial design and dosing regimens used have been in keeping with previous similar comparative studies (Table 6).

Table 6: Dosing Regimens

	Misoprostol	Dinoprostone
Frank J Chuck 1995	50µg 4 hourly	0.5 mg 4 hourly
Sanchez Ramos 1996	50µg 3 hourly	10 mg vaginal insert single dose
David Buser 1997	50µg 4 hourly	0.5 mg 6 hourly
Howard A Blanchette 1999	25µg 4 hourly	0.5 mg 6 hourly
Patrick S Ramsey 2003	50µg 6 hourly	0.5 mg 6 hourly
Sheela CN 2007	25µg 6 hourly	0.5 mg 12 hourly
GirijaShivarudraiah 2011	25µg 6 hourly	0.5 mg 6 hourly
Present study	25µg 6 hourly	0.5 mg 6 hourly

In the present study, both groups were matched in all respects to eliminate confounding factors. The demographic variables were similar in both groups. The mean maternal age was comparable to the studies conducted by Sanchez Ramos, Sheela NV and Girija Shivarudraiah.

The mean gestational age in the study cohorts was similar and comparable to those in all the underlisted studies (Table 7).

Table 7: Mean age (in years) and Mean gestational age (in weeks)

	Mean age (in years)		Mean Gestational age (in weeks)	
	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone
Frank J Chuck 1995	29.3	28.7	39.7	39.7
Sanchez Ramos 1996	24.4	23.1	38.8	38.7
David Buser 1997	27.7	27.1	39.2	39.3
Howard A Blanchette 1999	29.8	29.5	40.2	40.4
Patrick S Ramsey 2003	27.9	28.0	39.3	39.2
Sheela CN 2007	24.0	25.0	39.4	38.7
GirijaShivarudraiah 2011	25.0	25.0	39.4	39.4
Present study	24.9	26.4	38.6	38.9

The mean induction to vaginal delivery interval in our study was significantly shorter in the misoprostol group which was comparable to the studies conducted by Howard A Blanchette, David Buser and SheelaCN (Table 8).

Table 8: Induction to delivery interval (in hours)

	Misoprostol	Dinoprostone	Significence
Frank J Chuck 1995	11.4	18.9	S
Sanchez Ramos 1996	11.6	17.35	S
David Buser 1997	15.8	24.2	S
Howard A Blanchette 1999	19.8	31.3	S
Patrick S Ramsey 2003	23.9	31.1	S
Sheela CN 2007	15.2	22.0	S
GirijaShivarudraiah 2011	11.4	11.5	NS
Present study	12.6	15.6	S

The Cochrane Review on vaginal misoprostol for cervical ripening and induction of labour published in 2010 has set vaginal delivery not achieved within 24 hours as one of the five primary outcomes most reprehensive of the clinically important measures of effectiveness and complications.[94] This parameter is a useful benchmark as it provides a desired and realistically measureable end point of induction. In the present study, a significantly greater percentage of patients 94% delivered vaginally within 24 hours in the misoprostol group as compare to 74% in dinoprostone group. Similar findings are observed in the study by Ramsey. (Table 9).

Table 9: Vaginal delivery ion <24 housrs

	Misoprostol	Dinoprostone	Significance
Frank J Chuck 1995	100.0%	68%	S
Sanchez Ramos 1996	71.3%	60.9%	S
David Buser 1997	88.1%	49.3%	S
Howard A Blanchette 1999	71.9%	31.3%	S
Patrick S Ramsey 2003	60.5%	40.0%	S
Sheela CN 2007	83%	58%	S
GirijaShivarudraiah 2011	82,4%	58%	NS
Present study	94%	70%	S

The rate of caesarean section in another primary outcome measure employed by the 2010 Cochrane review for its sub group analyses of efficacy of vaginal misoprostol for cervical ripening for labour induction.[94] The rate of caesarean section in our study was similar in the two study cohorts, as is also stated in studies by Frank J. Chuck, Patrick S. Ramsey and Sheela CN. David Buser, Sanchez Ramos and Howard A. Blanchette have reported higher Caesarean rates in their studies, especially so in the misoprostol group. It is of note that these studies have used a higher dose (50 µg) of vaginal misoprostol and/ or a more frequent dosing regimen compared to the present study. The main indications for Caesarean section were fetal distress and failure to progress which were similar in the two groups in our study. Similar results have been quited in studies by Frank J. Chuck and Sanchez Ramos.

Table 10: Modes of Delivery

	Misoprostol		Dinoprostone		Significance
	NVD	CD	NVD	CD	
Frank J Chuck 1995	77%	20%	74%	20%	NS
Sanchez Ramos 1996	58,3%	22.2%	71.3%	13.05	NS
David Buser 1997	32.8%	35.5%	46.8%	21.5%	NS
Howard A Blanchette 1999		25.6%		22.32%	NS
Patrick S Ramsey 2003		14.3%		13.2%	NS
Sheela CN 2007	86%	14%	86%	14%	NS
GirijaShivarudraiah 2011	67.9%	25.2	66.5%	26.1%	NS
Present study	76%	24%	80%	20%	NS

(NVD- Normal Vaginal Delivery, CD – Caesarean delivery).

Researchers have employed various parameters to determine the success of induction. Howard A. Blanchette has used cervical dilatation >3 cm as the criterion for successful induction. Sheela CN defined failed induction as inability to go into labour or cervix not favourable enough for artificial rupture of membranes, at the end of the induction protocol. In the present study, successful induction was defined as the achievement of good uterine contractions (i.e. at least 3 contractions lasting for> 40 seconds in a 10 minute period) with the attainment of a Bishop's score of >5, similar to the criteria employed by David Buser. By this criterion alone, the rates of successful induction in the two groups are statistically similar in our study and this is in contrast with results quoted by David Buser where a highly significant trend towards more successful induction is seen in the misoprostol group (Table 11). However, other researchers such as Sanchez Ramos and Patrick S. Ramsey have used an induction to vaginal delivery interval of < 24 hrs to define successful induction.

Table 11: Rate of Successful induction (%)

	Misoprostol	Dinoprostone	Significance
David Buser 1997	68.4%	26.5%	S
Sanchez Ramos 1998	90.7%	67%	S
Howard A Blanchette 1999	96.6%	91.4%	NS
Patrick S Ramsey 2003	60.5%	40.0%	NS
Sheela CN 2007	98%	90%	NS
Present study	84%	90%	NS

In the present study, neonatal outcome with respect to birth weight, APGAR scores at 1 and 5 minutes, incidence of meconium stained liquor and NICU admissions was similar in the two groups. No neonatal deaths occurred either in the misoprostol group or dinoprostone group. The results were similar to the studies by Sanchez Ramos and Shivarudraiah. (Table 12).

Table 12. Neonatal Outcome

Study and Year	Misoprostol					Dinoprostone					Significance
	Birth weight (g)	APGAR <7 at 1 min (%)	APGAR <7 at 5 min (%)	Meconium (%)	NICU admission (%)	Birth weight (g)	APGAR <7 at 1 min (%)	APGAR <7 at 5 min (%)	Meconium (%)	NICU admission (%)	
Frank J Chuck 1995	3326	12%	0%	8%	10%	3331	8%	0%	10%	0%	NS
Sanchez Ramos 1996	3079	10.2%	0.9%	-	7.4%	3096	7%	1.7%	-	7.05%	NS
David Buser 1997	3435					3383				16.4%	NS
Howard A Blanchette 1999	3492	12.4%	1.4%	8.6%	8.6%	3583	11.1%	1.2%		6.2%	NS
Patrick S Ramsey 2003	3468					3436			7.9%	2.8%	NS
GirijaShivarudraiah 2011	2997	9.4%	1.8%	12.6%	0%	3006	5.0%	0.6%	11.8%	0.6%	NS
Present study	2792	4%	1%		1%	2775	3%	2%		2%	NS

RESULTS

Comparatively more women with misoprostol(52.4% vs 35.6%) achieved cervical ripening after the first dose. The mean Induction delievery interval was significantly shorter in the misoprostol group. In the misoprostol group 94.7% were deleivered within 24 hours as compared to 70% in the dinoprostone group. No significant difference found in the intrapartum complications and fetal outcome.

CONCLUSION

Tablet misoprostol 25 mcg is as effective as dinoprostone 3mg insert for cervical priming. Finding confirmed that it is as effective as dinoprostone for cervical ripening for induction of labour. It was found to have similar maternsal and fetal outcome. Use of misoprostol was found to be more cost effective than dinoprostone. This drug was well tolerated and therefore its use is recommended for cervical ripening for labour inductionin developing countries.

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