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Research Article – Medicine

Intravaginal administration of misoprostol alone versus misoprostol and isosorbidemononitrate for cervical ripening and labour induction

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Abstract

To compare the efficacy and safety of intravaginal administration of misoprostol alone versus misoprostol and isosorbide mononitrate for cervical ripening and labour induction. One hundred women with term gestation, Bishop score <4 with various indications for labour induction were randomly divided into two groups. In Group I, 50 µg of misoprostol tablet was placed intravaginally, 4 hourly maximum upto 4 doses. In Group II,50 µg of misoprostol tablet with 40mg of isosorbide mononitrate was placed intravaginally in posterior fornix upto 4 doses. Two groups were similar in their clinical characteristics. The induction to delivery interval was 20.8±2.9 hours vs 14.2±2.7 hours in two groups respectively. Misoprostol and isosorbide mononitrate was associated with a shorter induction to delivery interval, decreased oxytocin requirement higher rate of vaginal delivery i.e 62.8% Vs 53.9% . Uterine hyperstimulation was more common with misoprostol. Neonatal outcome was similar in both the groups. The present study suggests that both intravaginal misoprostol and combination of isosorbide mononitrate and misoprostol are safe and effective modes of labour induction. Isosorbide mononitrate and misoprostol is more effective than misoprostol alone in terms of shorter induction to active phase interval and induction to delivery interval.

Key words: Misoprostol, Labour Induction, Labour Augmentation, Isosorbide mononitrate, Cervical Ripening

Introduction

Induction of labour is now an integral part of modern day obstetrics. Several factors influence the outcome of induced labour. Unfavourable cervix is one of the main cause of failed induction, in order to overcome this cervix need to be ripened. Cervical ripening is an active process resembling an inflammatory reaction, which involves a complex cascade of degradative enzymes accompanied by degradation and disorganization of the collagen framework, an increased water content, and rearrangement of extracellular matrix proteins and glycoproteins [1,2]. Induction of labour with an unripe cervix is the main cause of induction failure and caesarean delivery. [3]Cervical ripening agents are routinely used in women with anunfavourable cervix which is often defined as Bishops score of ≤6. Ripening of the cervix may be achieved by both pharmacological and non-pharmacological (mechanical) methods [4]. Since the late 1960s prostaglandins (PG) have been used for the induction of labour at term. However, in the last years, there has been a considerable interest in the use of misoprostol [5,6,7] and nitric oxide (NO) donors [8,9] for cervical ripening and labour induction. Isosorbide mononitrate facilitate the production of nitric oxide to induce cervical ripening [10]. No donors may be such agent as they relax the myometrium while inducing

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cervical ripening. To the best of our knowledge, data regarding use of vaginal isosorbide mononitrate (IMN) and misoprostol for cervical ripening are limited and conflicting. Thus the present study was conducted to evaluate the efficacy and safety of intravaginal administration of misoprostol with isosorbide mononitrate versus misoprostol alone for cervical ripening and labour induction.

Materials and Methods

This prospective clinical study was conducted in the Department of Obstetrics and Gynaecology in collaboration with the Department of Paediatrics, J.N.M.C.H., A.M.U., Aligarh (U.P.) India during Sep 2014-Oct 2015. The included criteria were singleton pregnancy with cephalic presentation, gestation age> 37 weeks on the basis of LMP or first trimester ultrasonography, intact membranes, unfavourable cervix (Bishop score ≤ 4), need pregnancy termination for fetal or maternal indication. Women were excluded from the study if any of the following criteria were encountered: rupture of membranes, chorioamnionitis, antepartum haemorrhage, cervical dilation >2.5 cm, temperature >38ºC, contracted pelvis, fetal distress, polyhydramnios, indication for immediate delivery and previous caesarean section or other uterine surgery .One hundred women requiring indicated induction of labour with an unfavourable cervix (Bishop score ≤ 4) were included in the study. They were randomly divided into two groups. At first, the method of the study was completely explained to them if the written consent was obtained, they were enrolled in the study. This study was approved by the ethics committee of Faculty of medicine Aligarh Muslim University. Cases were selected from antenatal clinic (ANC), outpatient department (OPD) and patients admitted in the hospital. Demographic and clinical data were collected at routine antenatal visits. The two groups were comparable with respect to maternal age, parity, gestational age and preinduction Bishop score. In Group I, 52 women induced with 50 µg of misoprostol tablet which was placed intravaginally 6 hourly maximum upto 4 doses. In Group II, 50 µg of misoprostol tablet with 40 mg of isosorbide mononitrate was placed intravaginally in posterior fornix upto 4 doses. Patients was reevaluated after 6 hrs of initial application and based on the clinical response either no medication or a second dose of 50 µg of misoprostol or 40 mg isosorbide mononitrate and 50 µg of misoprostol was given in the two study respectively. The dose of drug was repeated every 6 hour until 3 or more uterine contractions of 40 secs duration occurred over 10 min or when the maximum of 4 doses (200 µg+160 mg) was reached. If there was no effective uterine contractions or patients not entering into active phase 6hrs after the fourth dose then it was considered as failure of induction and patient was taken up for caesarean section. Patient monitoring of fetal heart sound was done clinically or by cardiotocography. Fetal heart rate and uterine activity monitoring was done in accordance with the departmental protocol for induction of labor. Maternal pulse rate and blood pressure was taken every 30 mints during 2 hrs after initiation of treatment Augmentation was done either by artificial membrane rupture or oxytocin drip, whichever is indicated. Oxytocin drip (2.5 or 5 IU in 500 ml of Ringer's lactate solution) was started then and it was titrated according to frequency and intensity of uterine contractions. An oxytocin infusion was started at 2 mU/min and increased in increments of l-2 mU/min at 15-30-min intervals as needed to achieve an adequate contraction pattern. Maternal demographic profile, labour and delivery characteristics, adverse maternal effects and neonatal outcomes were examined. Data was analysed using SPSS software.

Results

In the present study, one hundred pregnant women with indication for induction were evaluated. They were randomly divided into two groups. 52 women induced with intravaginal misoprostol as Group I and 48 women induced with isosorbide mononitrate and misoprostol as Group II. Maternal baseline characterstics were similar between the two groups in terms of age, parity, gestational age

and preinduction Bishop score (Table 1)**.** The two groups were comparable with respect to indications for induction of labour (Table 2). Post induction Bishop score in two groups was 4.4 ± 1.6 and 8.2 ± 2.4 respectively. The Induction to active phase interval was 8.6±1.7 hours in misoprostol group and 5.6±1.7 hours in isosorbide mononitrate group and it was significantly shorter in group II. Oxytocin for labour augmentation was needed in 23.1% versus 22.9% and artificial rupture of membrane (ARM) was required in 50% versus 52.1% women in the two groups respectively. Induction to delivery interval was 20.8±2.9 hours in misoprostol group and 14.2±2.7 hours in isosorbide mononitrate plus misoprostol group and it was significantly shorter in group II.Vaginal delivery in misoprostol group was 53.9% and in isosorbide mononitrate and misoprostol group was 62.5%.The caesarean section rate was 46.1% in group I and 37.5% in group II, the mode of delivery was statistically non significant between the two groups Among the uterine contractile abnormalities the incidence of hyperstimulation was 3.8% in misoprostol group compared to 2.1% in isosorbide mononitarte and misoprostol group. There were no case of uterine tachsystole orhypertonus in both the study groups. Hypotension and tachycardia was reported in 4.1% women in isosorbide mononitrate and misoprostol group, and headache and flushing was reported in 2.1% women in isosorbide mononitrate and misoprostol group, while 5.7% women developed diarrhoea in misoprostol group. These maternal complications were statistically not significant in two groups as shown in Table 4.The birth weight was 2.84±0.44 and 2.87±0.42 in the two groups respectively. Apgar score at 1 minute was 7.3±1.5 versus 8.4±1.2 and at 5 minutes was 8.9 ± 0.4 versus 9.0±0.0 in both the groups respectively. NICU admission was 5.8% and 2.1% and meconium aspiration syndrome was noticed in 5.7% versus 2% in group I and group II respectively. Respectively but none of the neonate had any features suggestive of neonatal sepsis in either group (Table 5).

Table 1. Demographic profile of the study subjects

Parameters		Group I (n= 52) (Misoprostol)	Group II (n=48) (IMN and Misoprostol)	'p' value
Age (years) (Mean ±SD)		25.40 ± 4.3	24.10 ± 2.7	>0.05
Gravidity	Primi	46.1%	52.1%	>0.05
	Multi	53.9%	47.9%	>0.05
Gestational age (weeks) (Mean ±SD)		39.0 ± 1.58	38.79 ± 1.60	>0.05
Preinduction Bishop Score		2.4 ± 1.2	2.1 ± 1.2	>0.05

Table 2. Indication for induction of labour

Indication for induction	Misoprostol (n= 52)	IMN and Misoprostol (n=48)	'p' value
>40weeks	28(53.8)	19(39.5)	>0.05
Oligohydramnios	06(11.5)	04(8.3)	>0.05
Preeclampsia	09(17.3)	12(25.0)	>0.05
Intrauterine Growth Restriction	03(5.8)	01(02.1)	>0.05
Gestational Diabetes Mellitus	02(03.9)	03(06.3)	>0.05
Gestational Pruritis	01(1.9)	03(6.3)	>0.05
Others	03(5.8)	06(12.5)	>0.05
Total	52(100)	48(100)	-

Table 3. Labour outcome variables in the study groups

Parameters	Group I Misoprostol (n= 52)	Group II IMN and Misoprostol (n=48)	'p' value
Postinduction Bishop score	4.4 ± 1.6	8.2 ± 2.4	<0.001
Induction to active phase interval (Mean ± SD) (hrs)	8.6 ± 1.7	5.6 ± 1.7	<0.001
Augmentation Required	-	-	-
Oxytocin drip	23.1%	22.9%	>0.05
Oxytocin + ARM	50.0%	52.1%	>0.05
ARM	26.9%	25.0%	>0.0
Induction to delivery interval (Mean ± SD) (hrs)	20.8 ± 2.9	14.2 ± 2.7	<0.001
Mode of Delivery Vaginal	53.9%	62.5%	>0.05
Caesarean	46.1%	37.5%	>0.05

Table 4. Uterine contractile abnormalities and maternal side effects

Uterine contractile abnormalities	Group I Misoprostol (n= 52)	Group II IMN and Misoprostol (n=48)	'p' value
Tachysystole	0	0	-
Hypertonus	0	0	-
Hyperstimulation	2	1	>0.05
Maternal Side Effects			
Flushing	-	1	>0.05
Hypotension	-	2	>0.05
Tachycardia	-	2	>0.05
Headache	-	1	>0.05
Diarrhoea	3	-	>0.05

Table 5. Neonatal outcome in Group I and Group II

Parameters	Group I (n=52) (Misoprostol)	Group II (n=48) (IMN and Misoprostol)	'p' value
Birth weight (kg) (Mean ± SD)	2.84 ± 0.44	2.87 ± 0.42	>0.05
Apgar score (at 1 min) Mean ± SD	7.3 ± 1.5	8.4 ± 1.2	<0.001
Apgar score (at 5 min) Mean ± SD	8.9 ± 0.4	9.0 ± 0.0	<0.05
Admission in Neonatal intensive care unit	5.7%	2.0%	>0.05
Meconium aspiration syndrome	5.7%	2.0%	>0.05

Discussion

Induction of labour is an integral component of maternity practice and is frequently indicated for a variety of obstetric, medical, and social conditions. In this study the two groups were comparable in their demographic profile, preinduction Bishop score and indication for induction of labour. There is statistically significant difference in the postinduction Bishop score in both the groups DaveAnupama *et al.* [11] and Hamideh *et al.* [12] also found significant changes in the mean of Bishop score before and after IMN (1.94 ± 1.3 Vs 6.7±2.2) but differ from Wolfler MM, *et al.* [13] who found that vaginally administered IMN does not play a role in promoting delivery in pregnancy if given at the same time as dinoprostone. The results of the current study are not comparable because we use misoprostol instead of dinoprostone. Our findings are in consistence with Ahmed T Soliman [14] and Mohamad S. Abdellah [15] who demonstrated that the combination of IMN and misoprostol is more effective for cervical ripening than either IMN or misoprostol alone and results in a shorter latent phase of labour. The current study shows that the induction to delivery interval was significantly shorter in IMN and misoprostol group as compared to misoprostol alone group (14.2 ± 2.7 hours Vs 20.8 ± 2.9 hours, $p < 0.001$). The shorter induction to delivery interval in IMN and misoprostol group could be explained on the basis of synergistic effect on cervix via vaginal route due to direct access to cervix by cervical canal. Our results were in contrast with Justin P. Collingham, [16] as they did not show a benefit in the addition of vaginal isosorbide mononitrate to an oral misoprostol protocol for cervical ripening and labour induction in terms of reducing the length of time to vaginal delivery. The difference in the results could be due to route of administration of misoprostol as we have used vaginal in our study group as compared to oral misoprostol in their study. They chose to use oral misoprostolto eliminate the potential for pharmacologic interaction between vaginal misoprostol and vaginal isosorbide mononitrate. The lack of synergy between oral-misoprostol and vaginal isosorbide mononitrate may be a result of this effect.

Our findings are in agreement with the study of Ramya Krishnamurthy [17] as she also noted that the need for oxytocin was less in IMN group when compared to placebo group but statistically this also proved to be insignificant. misoprostol) but not in harmony with Abdul Razaq [18] regarding oxytocin need there is significant decrease in use of oxytocin for initiation or augmentation of labour ifmisoprostol was used for cervical ripening as it lead to development of uterine contractions. The mode of delivery was statistically non significant in two groups [14,16]. Uterine contractile abnormalities were more common in misoprostol group while nil in IMN and misoprostol group groups [15] here was no case of hyperstimulation in the IMN group in the study done by Habib *et al.* [19] but a higher incidence of tachysystole was observed in the IMN group which disagrees with our results. Maternal haemodynamic complications were more common in IMN and misoprostol group compared to misoprostol alone group and similar findings have also been reported by Kavita Agarwal[20] due to vasodilatory effect of nitric oxide donors.

Statistically there was no significant difference in the birth weight but the Apgar score between the two groups at 1 minute is statistically significant which is in harmony with the results reported by Abdul Razaq [18].

Conclusion

The present study suggests that both intravaginal misoprostol and combination of isosorbide mononitrate and misoprostol are safe and effective modes of labour induction. Isosorbide mononitrate and misoprostol is more

effective than misoprostol alone in terms of post induction Bishop Score, shorter induction to active phase interval and induction to delivery interval. Uterinehyperstimulation is more common with misoprostol while isosorbide mononitrate had no uterine contractile abnormalities. Isosorbide mononitrate and misoprostol is associated with better Apgar score at 1 minute and 5 minute respectively. Thus the combined use of nitric oxide donor (IMN) with misoprostol for preinduction cervical ripening at term may prove to be a major therapeutic advance.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors contributions: All authors contributed equally in writing, editing, proof reading the manuscript, the statistical analysis was done by Ambhika

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