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Original Research Article

Comparative study between vaginal isosorbide mononitrate and misoprostol for induction of cervical ripening prior to first trimester surgical abortion

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ABSTRACT

Background: To evaluate the efficacy of the tab. isosorbide mononitrate 80 mg and tab. misoprostol 400 µg given transvaginal for cervical ripening before surgical evacuation in early embryonic demise upto 12 weeks of gestation (missed abortion).
Methods: The present randomized controlled trial was conducted in Bebe Nanaki mother and child care centre, attached to govt. medical college, Amritsar, from August 2011 to September 2013 after approval of institutional research committee. All the 50 women were included after obtaining a written consent, and after proper history taking and examinations and were allocated randomly into two groups. In group A patients, tab. isosorbide mononitrate 80 mg was given and in group B patients, Tab. Misoprostol 400ug was given up to maximum of four doses until cervical dilatation of >8 mm has been achieved. Lack of cervical dilatation >8 mm after the 4th dose of medication was considered as a failure of treatment.
Results: In this study, the success rate was more with tab. misoprostol group (96%) as compared to tab. isosorbide mononitrate group (80%), whereas the failure rate with tab. misoprostol group was 4% and with tab. isosorbide mononitrate group was 20%. Cervical ripening with tab. misoprostol was rapid with less frequency of dosage and less induction to ripening interval. Specific side effects are there for both the groups.
Conclusions: In our study we observed that, tab. misoprostol appeared to be more effective than tab. isosorbide mononitrate.

Keywords: Cervical ripening, Missed abortion, Nitric oxide donor, Surgical evacuation, Misoprostol

INTRODUCTION

The human uterine cervix is a complex and heterogeneous organ that undergoes extensive changes throughout gestation and parturition. It has a unique value responsible for keeping the foetus inside the uterus until the end of gestation and for its safe passage to the outside world during the labour.

The exact processes through which the final stage of cervical ripening occurs to allow effacement and dilatation are still unclear.

Role of prostaglandins, cyclooxygenases and nitric oxide in cervical ripening

Prostaglandins, especially PGE2, have for a long time been thought of as key mediators of cervical ripening by causing dilatation of cervical vessels and extravasation of leukocytes.[1,2]

Cyclooxygenase (COX) is the rate-limiting enzyme in the biosynthesis of PGs. In addition to the well characterized constitutive form of COX-1, an inducible isoform of COX-

2 is found in endothelial cells, fibroblasts and macrophages.[3-7]

COX-2 is typically undetectable in most tissues under normal physiological conditions but can be expressed at high levels following stimulation. A recent study has shown that there is an increase in cerivical COX-1 and COX-2 at parturition.[8] Moreover, from several studies conclusions have been made that PGs can stimulate the release of nitric oxide (NO).[9]

Nitric oxide is involved in regulating many factors in the inflammatory process of cervical ripening.

Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1 and because of its uterotonic and cervical ripening activity, wide ranging off label uses have been found for misoprostol, and it has been described as “one of the most important medications in obstetrical practice.”

Misoprostol is now a legitimate part of the FDA approved regime for use with mifepristone to induce abortion in early pregnancy and is also recognizes for its use for induction of labour.

METHODS

The present randomized controlled trial was conducted in Bebe Nanaki mother and child care center, attached to govt. medical college, Amritsar, from August 2011 to September 2013 after approval of institutional research committee. After receiving proper written consent, all the patients were subjected to a history taking and examination at the time of admission. The patients who were having the First trimester missed abortion with ultrasound evidence of a gestation sac and non-viable embryo with closed Internal os without any history of hypotension. While women with unexplained vaginal bleeding, one with first trimester embryonic demise already in the process of expulsion or women with any contraindication to use of isosorbide mononitrate and misoprostol like cardiac disease or hypersensitivity to these drugs.

Participants were allocated randomly into two groups. In group A patients, tab. isosorbide mononitrate 80 mg was placed in posterior vaginal fornix and dose was repeated every three hourly, up to maximum of four doses or until reaching cervical ripening (cervical dilatation >8 mm). The maximum dose of isosorbide mononitrate was 320 mg.

In group B patients, tab. misoprostol 400 ug was placed in posterior vaginal fornix, every three hourly, up to maximum of four doses or until reaching cervical ripening (cervical dilatation >8 mm). The maximum dose of misoprostol was 1600 ug.

Cervical dilatation was assessed at baseline and every three hours. If the cervical dilatation remains below 8 mm after three hours of treatment administration, the participating subject received another dose up to a total of four doses to produce cervical ripening.

Once the cervical dilatation of >8 mm achieved, evacuation of the product of conception was done.

Lack of cervical dilatation >8 mm after the 4th dose of medication was considered as a failure of treatment.

The participant was asked to answer a symptom questionnaire before and during the administration of the intervention. Headache, abdominal pain, pelvic pain, backache, nausea and vomiting, dizziness, palpitation, diarrhoea, vaginal bleeding was asked. Patients were asked to respond "yes" or "no" to the question and their response was recorded.

Peripheral heart rate and blood pressure recording was done on admission, during treatment and prior to surgical evacuation.

Mean and standard deviations were calculated for quantitative variables i.e. age, parity, duration of gestation, induction to ripening interval and intra-operative blood loss and independent sample t-test was used to compare these variables. Chi-square was used to compare distribution of subjects based on parity, gestational age, uterine size, distribution of doses, induction to ripening interval, incidence of each new symptoms i.e. headache, abdominal pain, pelvic pain, backache, nausea and vomiting, need for uterotonic agent and percentage of successful and failed induction. P value obtained, p value less than 0.05 was taken as significant.

RESULTS

The mean age of subjects in group A was 25.32±3.02 and in group B mean was 25.68±3.06 years. Age was comparable in both the groups as shown in Table 1. Distribution of subjects on the basis of parity was comparable in both group (p>0.05) are shown in Table 2. The mean gestational age at which embryonic demise occurred according to USG in group A was 7.40±1.48 (weeks) and in group B was 8.04±1.85 (weeks), which was comparable in both the study groups (p>0.05) (Table 3).

Both the drugs were used until the cervical ripening or up to maximum of 4 doses, the frequency of doses as shown in Table 4 was relatively higher in group A (tab. isosorbide mononitrate) and having significant p=0.026.

The highest dose frequency that was used in group A was three doses which were used in 9 (36%) patients followed by two doses and four doses which were used in 6 (24%) patients each. While only 4 (16%) patients used a single dose.

But in group B (tab. misoprostol), highest frequency was one dose. In 12 (48%) patients, the required cervical dilatation was achieved after a single dose of misoprostol followed by two doses which were used in 8 (32%) patients and three doses which were used in 3 (12%) patients and only 2 (8%) patients used four doses.

Mean induction to cervical ripening interval in group A (Tab. isosorbide mononitrate) 7.50±2.89 hours. In group B (Tab. misoprostol), mean induction to ripening interval was 5.08±2.67 hours (Table 5). Analysis of data showed that mean induction to ripening interval was significantly higher in group A as compared to group B ($p<0.05$).

Table 1: Mean age (years) of study subjects in both study groups.

Mean age of subject (in years)	Group A (Tab. isosorbide mononitrate)	Group B (Tab. misoprostol), (n=25)	T value	P value
	25.32±3.02	25.68±3.06	-0.186	0.854

Table 2: Distribution of subject based on obstetrical history.

Parity	Total no. of subjects, (n=50)		Group A, (n=25)		Group B, (n=25)	
	N	%	N	%	N	%
Gravida I	19	38.0	9	36.0	10	40.0
Gravida II	16	32.0	8	32.0	8	32.0
Gravida III	10	20.0	6	24.0	4	16.0
Gravida IV	5	10.0	2	8.0	3	12.0
Total	50	100.0	25	100.0	25	100.0

Table 3: Mean gestational age (weeks) at which embryonic demise occurred according to USG of study groups.

Mean gestational age (weeks)	Group A (Tab. isosorbide mononitrate)	Group B (Tab. misoprostol), (n=25)	T value	P value
	7.40±1.48	8.04±1.85	1.331	0.189

Table 4: Distribution of doses in study groups.

No. of doses	Total no. of subjects, (n=50)		Group A, (n=25)		Group B, (n=25)	
	N	%	N	%	N	%
1	4	16.0	12	48.0	16	32.0
2	6	24.0	8	32.0	14	28.0
3	9	36.0	3	12.0	12	24.0
4	6	24.0	2	8.0	8	16.0
Total	25	100.0	25	100.0	50	100.0

Table 5: Comparison of mean induction to ripening interval (hours).

Drug group	Mean interval (hours)	SD	T value	P value
Group A, (n=25)	7.50	±2.891	2.948	0.048
Group B, (n=25)	5.08	±2.669		

Table 6: Percentage of successful and failed induction in both groups.

Variables	Group A, (n=25)		Group B, (n=25)		P value
	N	%	N	%	
Successful induction	20	80.0	24	96.0	$>0.05^{NS}$
Failed induction	5	20.0	1	4.0	

NS-Not significant.

As shown in Table, in group A, 20 (80%) patients achieved successful induction after tab. isosorbide mononitrate while 5 (20%) patients failed to achieve cervical dilatation>8 mm even after consecutive 4 doses of tab. isosorbide mononitrate.

In group B 24 (96%) patients achieved successful induction after tab. misoprostol while 1 (4%) patient failed to achieve cervical dilatation>8 mm even after consecutive 4 doses of tab. misoprostol. Analysis of the data showed that number of failed inductions were higher with tab. isosorbide mononitrate compared to tab. misoprostol [5

(20%) patients v/s 1 (4%) patient] but results were non-significant (p 0.082) in group A, intraoperative need of uterotonic agent was required in 5 (20%) patients and 20 (80%) patients didn't require uterotonic support. In group B, 4 (16%) patients required intraoperative uterotonic support while 21 (84%) patients didn't require intraoperative uterotonic support. These results were comparable in both study group after analysis of data ($p>0.05$).

The post operative course was uncomplicated in all patients with no evidence of infection or retained products of conception. Although two patients with misoprostol group required 1 day in hospital due to abdominal and pelvic pain. 6 patients in whom cervix didn't dilate following treatment (5 patients who received isosorbide mononitrate and 1 patient who received misoprostol) required dilatation with Hegar dilator after 12 hours to ease extraction of products of conception. None of them showed spontaneous expulsion of the products.

Side effects

Significantly higher number of women given tab. isosorbide mononitrate experienced headache when compared with women treated with tab. misoprostol [7 (28%) patients v/s no patient ($p<0.05^{S}$)]. Abdominal pain occurred with both drugs. But was non-significantly higher in tab. misoprostol treated group then tab. isosorbide mononitrate treated group [6 (24%) patients v/s 3 (12%) patients ($p>0.05^{NS}$)].

Nausea and vomiting observed with tab. misoprostol treated group is non-significantly more than tab. isosorbide mononitrate treated group [2 (8%) patients v/s no patient ($p>0.05^{NS}$)].

Palpitation was observed with tab. isosorbide mononitrate treated group, in 1 (4%) patient v/s no patient in tab. misoprostol group ($p>0.05^{NS}$).

Number of the patients who developed vaginal bleeding were non significantly higher in tab. misoprostol treated group [4 (16%) patient vs 2 (8%) patients ($p>0.05^{NS}$)].

Incidence of backache was comparable in both study groups (2 (8%) patients v/s 2 (8%) patients).

DISCUSSION

The present study shows that tab. misoprostol (400 ug) induced a more rapid cervical dilatation as compared to tab. isosorbide mononitrate (80 mg), the induction to ripening interval was significantly higher in tab. isosorbide mononitrate pretreated group A as compared to tab. misoprostol pretreated group B.

Shafique et al showed that mean induction to ripening interval in group A was 8.03±2.80 hours and in group B was 4.47±2.04 hours.[11]

Ledingham et al revealed that the mean induction to ripening interval in group A was 2.50 hours while in group B interval was 2.81 hours.[12]

Table 7: Interval with highest frequency in different studies (hours).

Authors	Group A (Tab. isosorbide mononitrate)	Group B (Tab. misoprostol)
Shafique et al[11]	6	3
Arteaga-Troncoso et al	3	6
Ledingham et al[12]	9	3
Present study	9	3

Table 8: Mean induction to ripening interval in different studies (hours).

Authors	Group A (Tab. isosorbide mononitrate)	Group B (Tab. misoprostol)
Shafique et al[11]	8.03±2.8	4.47±2.04
Ledingham et al[12]	2.50	2.81
Present study	7.50±2.90	5.08±2.67

The present study shows that the highest dose frequency, used in tab. isosorbide mononitrate, 3 doses, which were used in 36% of the patients followed by 4 doses in 24% of the patients while the highest dose frequency used in tab. misoprostol treated group was single dose used in 48% of the patients followed by 2 doses in 32% of the patients.

Shafique et al concluded that the highest dose frequency in group A and group B was 2 doses and single dose respectively, which was used in 32% of the patients and 52% of the patients respectively.[11]

Thomson et al showed that tab isosorbide mononitrate could be used as an alternative of tab misoprostol for cervical ripening before surgical procedures in first trimester embryonic demise.[13,14]

Duhan et al according to this study mean size of dilator that could be negotiated without any resistance was 5.9±1.33 mm in group A (tab. isosorbide mononitrate) and 8.6±0.94 mm in group B (tab. misoprostol) ($p<0.001$). The mean dilator sizes at which resistance was first encountered was 6.9±1.37 in group A and 9.9±1.23 in group B ($p<0.001$). The results showed that tab. isosorbide mononitrate had definitive role although the misoprostol was more effective.[15]

In our study we observed that tab. misoprostol appeared to be more effective than tab. isosorbide mononitrate. Cervical ripening with tab. misoprostol was rapid with less frequency of dosage and less induction to ripening interval. In group A, 20 (80%) patients achieved successful

induction after tab. isosorbide mononitrate while 5 (20%) patients failed to achieve cervical dilatation >8 mm after 12 hours. In group B, 24 (96%) patients achieved successful induction after treatment with tab. misoprostol while 1 (4%) patient failed to achieve cervical dilatation >8 mm after 12 hours of treatment. Number of failed inductions were higher with tab. isosorbide mononitrate than tab. misoprostol treated group, but these results were not. significant (p>0.05).

Radulovic et al showed that in both treatment groups, the frequency and intensity of the side effects gradually increased during the interval. Common side effects of tab. misoprostol were abdominal pain (69%), nausea (44%), vaginal bleeding (66%) while in tab. isosorbide mononitrate group headache was frequently experienced (79%).[16]

El Khayat et al showed that there was no significant difference between tab. isosorbide mononitrate and tab. misoprostol group regarding nausea, vomiting and hot flushes. In contrast there was a significant difference between tab. isosorbide mononitrate and tab. misoprostol regarding abdomen pain (17 patients v/s 55 patients) and headache (65 patients v/s 9 patients).[17]

The present study also showed that there was no significant difference in number of the patients, who required, intraoperative uterotonic agent in both study group [5/25 (20%) patients in group A v/s 4/25 (16%) patients in group B.

Limitation

The study size was small and was performed at tertiary care center.

CONCLUSION

Based on the results of the present study we concluded that the benefits of misoprostol are greater than its side effects, so it is a better cervical ripening agent prior to suction evacuation of first trimester embryonic demise with acceptable side effects. Use of tab. misoprostol for cervical ripening reduces the induction to ripening interval leading to early surgical evacuation and shorter hospital stay. Success rate was more with tab. misoprostol group (96%) as compared to tab. isosorbide mononitrate group (80%), whereas the failure rate with tab. misoprostol group was 4% and with the tab. isosorbide mononitrate group was 20%.

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