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Vaginal Isosorbide Mononitrate and Misoprostol for Induction of Cervical Ripening Prior to 1st Trimester Surgical Evacuation of Retained Products of Conception

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Abstract

Background: **To compare the effect of vaginal isosorbide mononitrate with misoprostol for cervical ripening in women with first trimester missed abortion before surgical evacuation of uterus.**

Methods: **In this randomized controlled trial, hundred patients, requiring cervical ripening and surgical evacuation of retained products of conception, were divided into two equal groups. Misoprostol (400 microgram) was placed in posterior vaginal fornix in Group A patients and dose was repeated every three hours upto 4 doses or until reaching cervical ripening. Isosorbide mononitrate (80milligram) was given vaginally in Group B patients and dose was repeated every three hours up to 4 doses or until reaching the cervical ripening.**

Results: **There was no significant difference in side effects between two groups. However Misoprostol was more effective than Isosorbide Mononitrate (IMN) to cause cervical ripening before suction termination of first trimester missed abortion .**

Conclusion: **Nitric oxide donor "Isosorbide mononitrate" is less effective than "Misoprostol" to induce cervical ripening prior to first trimester surgical evacuation of retained products of conception and both drugs are associated with a high frequency of side effects.**

Key Words: **Cervical Ripening, Missed abortion, nitric oxide donor, misoprostol.**

Introduction

The uterine cervix has to be firm enough to retain the conceptus through the pregnancy and on the other hand have the ability to soften before and during labour to enable the birth of infant. Cervical ripening and maturation is very important pre-requisite for the successful termination of pregnancy.[1]

Two major techniques for iatrogenic cervical ripening are mechanical intervention such as disruption of fetal membranes or insertion of dilators and application of cervical ripening agent such as prostaglandin.[2] However prostaglandins are associated with side effects such as nausea, vomiting, diarrhoea, abdominal cramps, chills, shivering and uterine hyperstimulation.[3]

Nitric oxide releasing drugs are the novel class of effective and safe drugs for cervical ripening.[4,5] It has been shown to be a major paracrine mediator of numerous biological processes including smooth muscle relaxation, host defence and inflammation. [6] Cervical ripening is thus associated with changes in local cytokines, prostaglandins and metalloproteases as well as in other bioregulators that play role in inflammation and in collagen metabolism.[7] These factors also take part in regulation of nitric oxide synthesis and release. [8] Several chemical donors of nitric oxide are currently being used in various types of experimental and therapeutic studies. [9]

Patients and Methods

In this randomized controlled trial, all patients admitted through OPD and emergency of Gynae / Obstetrics unit of DHQ Teaching hospital, having ultrasound evidence of a gestation sac and a non-viable embryo requiring cervical ripening and surgical evacuation of retained products of conception, were included. Women with unexplained vaginal bleeding or discharge, with any contraindication to use of isosorbide mononitrate, cardiac disease or hypersensitivity to the drug and cervical dilatation more than 8mm were excluded from study. Vaginal examination was carried out at the time of admission to assess cervical ripening

Randomization was done (lottery method) and double blind technique was applied to decrease observer bias and patient bias.In group A patient's 400 micro gram of misoprostol was placed in posterior vaginal fornix every 3 hrs up to four doses or until reaching cervical ripening. The maximum dose of

misoprostol was 1600 microgram. In group B patient's 80mg of isosorbide mononiterate was given vaginally and dose was repeated every three hrs up to four doses or until reaching cervical ripening. The maximum dose of isosorbide mononitrate was 320mg.

During this procedure vital signs, symptoms and adverse effects were recorded at base line and then every 3 hrs until finishing therapy. Time of 1st, 2nd, 3rd and 4th dose of tablet was noted and induction – ripening interval was recorded. If cervical dilatation was more than or equal to 8mm, then surgical evacuation of retained products of conception was performed.

Mean and standard deviations were calculated for quantitative variables i.e. induction-ripening interval, age, parity, duration of gestation and cervical score. Frequencies and percentages were calculated for qualitative variables such as headache, abdominal pain, pelvic pain, backache, nausea and vomiting. Independent sample t-test was used to compare induction-ripening interval between isosorbide mononitrate and misoprostol. Chi-square test was used to compare the side effects.. P value less than 0.05 was taken as significant.

Results

In isosorbide mononitrate (IMN) group the mean age was 27.52 ±5.168 years ranging from 18 to 40 years and in Misoprostol group the mean age was 28.26±5.244 years. The gestational age in both groups was almost same .The parity distribution showed that in IMN group 28% were primipara 52% were multi para and 20% were grand multi para. In Misoprostol group 10% were primipara, 82% were multipara and 8% were grand multipara.

Both the drugs were used as until the ripening, the frequency of doses was relatively higher in IMN group. The highest dose frequency that was used in Misoprostol group was 1. In 29 patients the required level was achieved after 1 dose of Misoprostol but in the IMN group the highest frequency of doses used was 2 doses which were used in 19 patients followed by 4 doses which were used in 17 patients as given in (Table 1).

In Misoprostol group the interval with highest frequency was 3 hours at which 30 (59%) patients achieved the required level. This interval was comparatively higher in IMN group in which the interval at which the required level was achieved was 6 hours (32%), followed by 9 hours (26%) as given in Table 2. The analysis of data showed that the mean induction to ripening interval was significantly (8.03±2.833 vs. 4.47±2.042, P-value < 0.05) higher in IMN group as compared with Misoprostol group, which is shown in Table 3.

Table 1:Distribution of Doses in both Groups

No. Of Doses	Drug Group		Total
	IMN	Misoprostol	
1	6	29	35
2	19	7	26
3	8	11	19
4	17	3	20
Total	50	50	100

Table 2: Induction to ripening interval

Drug Group	Induction to ripening interval	Frequency	Percent
Misoprostol	No Effect	3	6.0
	3	29	58.0
	6	13	26.0
	9	5	10.0
	12	0	0
	Total	50	100.0
IMN	No Effect	8	16.0
	3	4	8.0
	6	16	32.0
	9	13	26.0
	12	9	18.0
	Total	50	100.0

Table 3:Comparison of Induction to Ripening Interval (hours)

Drug Group	Mean	Std. Deviation	P-value
IMN	8.03	2.833	0.000
Misoprostol	4.47	2.042	

In side effects profile headache was significantly high in IMN group than Misoprostol group (p-value 0.05). There was no significant difference in hypotension in both groups (p-value <0.05). Abdominal pain was significantly higher in Misoprostol group as compared to IMN group (p-value<0.05) .The backache was same in both groups (p-value>0.05). The nausea was only observed in Misoprostol group (p-value <0.05) that was

significantly higher as compared to IMN group. The results also show that vomiting was higher in Misoprostol group as compared to IMN group (Table 4).

Table 4:Comparison of side effects

Side Effects	Misoprostol	IMN	P-Value
Headache	06	30	0.00
Hypotension	00	2	0.153*
Abdominal Pain	06	1	0.05*
Backache	5	5	1.00*
Nausea	8	0	0.003
Vomiting	4	0	0.041*

Discussion

The present study showed that misoprostol (400 microgram) induced a more rapid cervical dilatation as compared to Isosorbide mononitrate (80mg). The induction - ripening interval was significantly higher in IMN group as compared to Misoprostol group. In Misoprostol group the interval with highest frequency was 3 hours at which 29(58%) patients achieved required level. This interval was comparatively higher in IMN group in which the interval at which required level was achieved was 6 hours (32%) followed by 9 hours (26%). Similarly the frequency of doses was relatively higher in IMN group. The highest dose frequency, which was used in Misoprostol group, was 1 in 29 patients while in IMN group the highest dose frequency was 2 doses, which were used in 19 patients followed by 4 doses, which were used in 17 patients. The poor clinical response of IMN in above-mentioned study and in our study is difficult to explain. It is unlikely that dosage of IMN has any major effect as a higher dose of IMN (80mg) gave the same ripening effects as 40mg of IMN.

The side effects were more frequently seen in our study which may be due to the fact that we used maximum 4 doses of each drug in our patients where as in studies with less side effects single dose of each drug was used. Another study was published in 2008 on the side effects of vaginal application of IMN, Misoprostol and DILAPAN-S, a hygroscopic cervical dilator prior to first trimester curettage. This study showed that all patients indicated mild discomfort after DILAPAN where as no patient complained of discomfort after Misoprostol or IMN (P<. 0001). 3 patients suffered from mild hypotension and headache after IMN and 2 had increased vaginal bleeding due to uterine atony during surgery (p<0.05). In this study 80mg of IMN and 200microgram of Misoprostol vaginal gel was used to cause cervical ripening. [10]

Conclusion

1. Benefits of Misoprostol are greater than its side effects so it is a better cervical ripening agent prior to suction evacuation of first trimester missed abortion with acceptable side effects.
2. Use of Misoprostol for cervical ripening reduces the induction to ripening interval leading to early surgical evacuation and short hospital stay.

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