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Original Article

Comparison of different regimes of misoprostol for the termination of early pregnancy failure

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ABSTRACT

Background: Nearly 20% of all confirmed pregnancies end in spontaneous abortion. Misoprostol's use in early pregnancy failure is varied and dose and route are not well established. The aim of this study was to compare the efficacy and the side effects of different regimes of misoprostol in causing expulsion of products of conception in early pregnancy failure.

Method: Women patients with an ultrasound diagnosis of early pregnancy failure, less than 12 weeks gestation were divided into two, Group-A: tab. Misoprostol 800 mcg 6 hourly vaginally, upto 3 doses. Group-B tablet misoprostol 600 mcg 6 hourly, sublingually for 3 doses. All observations were noted and statistical analyzed.

Results: Mean gestational age was 7.93 weeks. Mean induction abortion interval 18.183 h. Women patients with less than six weeks gestational age had least mean induction-abortion interval time, 15.75 ± 2.82 h in vaginal group but was highest in sublingual group 22 ± 2 h and 18.43 h in overall ($P = 0.02$). Though after 8 weeks, both routes were equally effective. Mean dose required in group-A was 20044 mcg and in group-B was 1564 mcg ($P < 0.001$). Efficacy of protocol was 88.89% in group-A and 92.85% in group-B.

Conclusion: Both regimes had comparable efficacy, acceptability (90%) and side effects. In women patients less than six weeks period of gestation, the vaginal (800 mcg) route was distinctly superior, in women patients with 6–8 weeks the sublingual (600 mcg) route was more advantageous. The correct dose must be used for the route chosen. The route of administration should be decided in accordance with the preference of the patient and the clinical situation.

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Introduction

Early pregnancy failure is common and represents a significant gynecological emergency workload. Nearly 20% of all confirmed pregnancies end in spontaneous abortion.¹ The conventional method of uterus evacuation by vacuum aspiration is associated with morbidity and mortality. The use of prostaglandins PGE₂ vaginally had replaced the surgical methods due to their ease of administration, high effectiveness and fewer complication.² However, the high expense of the medicine and instability in room temperature were barriers to their use in developing countries. Misoprostol – a synthetic prostaglandin E₁ analog, is cheap, stable at room temperature and effective in inducing cervical ripening and uterine contractions.³ However, the regimes for its use in early pregnancy failure are varied and not well established. Earlier clinical trials had shown vaginal misoprostol to be superior. Misoprostol given vaginally though took longer for onset and had a lower peak (peak concentration after 60 minuet it had a more sustained effect as compared to oral misoprostol). Thus, smaller doses were needed when misoprostol was used vaginally. Pharmacokinetics now shows that sublingual misoprostol has the shortest onset of action, the highest peak concentration and greatest bioavailability among the routes of administration.⁴ As the bioavailability varies with each route, the correct dose must be used for the route chosen e.g. sublingual to oral or vaginal and route should not be changed without checking the dose. The aim of this study was to compare the efficacy and the side effects of different regimes of misoprostol in causing the complete expulsion of products of conception in early pregnancy failure.

Material and methods

This was a comparative; hospital based prospective study conducted from April 2012 to May 2013. Women patients with an ultrasound diagnosis of early pregnancy failure, singleton pregnancy, less than 12 weeks gestation, who had not experienced uterine cramping, no active bleeding (os closed on per vaginal examination) and were in a normal frame of mind to give consent and willing for a surgical evacuation in case of failure with medication or active bleeding, were included in the study.

The USG criteria used for diagnosis of early pregnancy failure (missed abortion) were-embryo with CRL greater than 7 mm with no cardiac activity or irregular gestational sac with mean sac diameter greater than 16 mm or a gestational sac more than 25 mm with no visible fetal pole.⁵

Sample size was calculated at 80% study power and alpha error of 0.05 assuming standard deviation for duration of induction to abortion interval of 5 h and minimum difference to be detected of 2 h. Thus sample size came to be 50 patients in each group which was enhanced 55 assuming 10% dropout rate.

Group allocation after counseling and informed written consent, the women patients were divided into two groups using coin tossing method and allocated for treatment with either regimes.

Group-A: In this group women patients were given vaginal – tablet misoprostol 800 mcg every 6 hourly upto 3 doses.

Group-B: In this group women patients were given sublingual-tablet misoprostol 600 mcg every 6 hourly for 3 doses. The dose was decreased to lessen the side effects.

Evaluation was done 6 h after 3rd dose of misoprostol, i.e. at 24 h. If the uterus was not felt empty on per vaginal examination and ultrasonography showed products of conception, then dilatation and evacuation was done and was considered a true drug failure.

Data analysis and processing: Collected data was entered into a computer using Epi Info Version 2000 and analyzed using Medcalc 14.0.0 version and Microsoft excel. Continuous data was presented as mean and standard deviation while non-continuous data was categorized and the percentage of each category was calculated. Chi-square was used to test for association. A P value less or equal to 0.05 was considered indicative of a significant factor effect.

Results

The mean age of women patients in the study was 24.18 ± 5.1 years. Majority of the women patients were educated up to primary level or less and 80% were from urban background. Due to the use of misoprostol at PHC and CHC, referrals to tertiary care center like ours for early pregnancy failure have decreased. 90% of the cases in both the groups belonged to middle and lower middle class Table 1.

71.81% women patients came with complaints of bleeding per vaginum. 28.18% women patients had come for routine checkup and USG had shown missed abortion. 9.09% women patients came with pain abdomen and 3.64% women patients came with brownish discharge. 79.09% of the women patients had fetal pole absent or irregular gestational sac in the ultrasonographic findings. The other finding was a blighted ovum seen 20.91%.

Mean gestational age was 7.93 ± 1.2 weeks. Mean induction abortion interval was similar in the two groups, 18.125 h in group-A and 18.241 h in group-B. Women patients with less than six weeks gestational age in group-A, had least mean

Table 1 – Maternal and gestational characteristics of the study population.

Variables	800 mcg	600 mcg
Maternal age (years)	24.57 (± 5.1)	23.79 (± 5.2)
Literacy primary or less	27 (49.99%)	27 (49.08%)
Primigravida	19 (35.18%)	21 (37.5%)
1 previous vaginal deliveries	24 (44.44%)	24 (42.86%)
2 or more previous vaginal deliveries	11 (20.38%)	11 (19.64%)
Presenting complaint – bleeding P/V	38 (70.37%)	41 (73.21%)
Gestational age (weeks)	7.905 (± 1.2)	7.946 (± 1.3)
Anembryonic sac	10 (18.52%)	13 (20.91%)

Maternal age and gestational age are expressed as the mean (SD). All other parameters are shown as number (percentages). No significant differences were observed between the two groups.

Table 2 – Correlation of gestational age and mean induction-abortion interval time.

Gestational age (in wks)	Group-A		Group-B		Total		T test
	No.	Mean induction-abortion interval Time $\pm$ SD	No.	Mean induction-abortion interval Time $\pm$ SD	No.	Mean induction-abortion interval Time $\pm$ SD	P value
Less than 6	4	15.75 $\pm$ 2.82	3	22 $\pm$ 2	7	18.43	0.02S
06–08	33	18.84 $\pm$ 2.37	34	17.38 $\pm$ 2.86	67	18.10 $\pm$ 4.08	0.02S
08–10	11	18.18 $\pm$ 3.94	14	18.42 $\pm$ 3.45	25	18.32 $\pm$ 3.60	0.8NS
10–12	6	16.67 $\pm$ 3.26	5	20 $\pm$ 2.55	11	18.18 $\pm$ 3.31	0.09NS
Total	54	18.24 $\pm$ 2.96	56	18.12 $\pm$ 3.14	110	18.18 $\pm$ 3.04	0.84NS

induction-abortion interval, 15.75 $\pm$ 2.82 h. Women patients with less than six weeks gestational age in group-B had the highest mean induction-abortion interval, 22 $\pm$ 2 h. In women patients with gestational age six to eight weeks mean induction-abortion interval time 18.84 $\pm$ 2.37 h in group-A and 17.38 $\pm$ 2.86 h in group-B. These differences were statistically significant ($P = 0.02$ in both). After 8 weeks, both schedules were equally effective [Table 2](#).

Mean dose required in group-A was 2044 mcg and in group-B was 1564 mcg and though this was statistically significant ($P < 0.001$); the efficacy was comparable in the two groups –88.89% in group-A and 92.85% in group-B. Level of satisfaction and acceptability too were similar in the two groups [Table 3](#).

Although most of women patients experienced some side effects, they found them tolerable and were comparable in the two groups. Abdominal pain was reported by almost all cases but analgesics were required by only 27.78% in group-A and 32.14% in group-B. Other frequently reported adverse effects requiring treatment were vomiting (3.70% in group-A and 10.71% in group-B), diarrhea (7.41% in group-A and 8.93% in group-B), fever/chills (3.70% in group-A and 10.71% in group-B), headache (1.85% in group-A and 5.36% in group-B), allergy (3.70% in group-A and 5.36% in group-B) [Table 4](#).

On follow-up visit, most women patients had no complaints and none required evacuation.

Szymanska et al¹⁰ used 400 mcg of vaginal misoprostol for termination of missed abortion with only 30.3%, success for achieving complete abortion, since this dose was too small. Suguna et al¹¹ managed missed abortion by a lower dose of 400 μ g vaginal misoprostol 4 hourly to a maximum of 3 doses. Successful complete medical evacuation occurred in 86% but completely failed in 7.3%. Francisco et al¹² used 800 versus 600 mcg of vaginal misoprostol to compare the effectiveness. The total rate of complete evacuation was 90.6% after 800 mcg and 87.8% after 600 mcg of intra vaginal misoprostol as compared to 88.89% with 800 mcg misoprostol in our Ngoc study. Ngoc et al¹³ had compared the efficacy of oral and vaginal Misoprostol (800 mcg for both) for treatment of missed abortion. The two groups did not differ in terms of the completion rate but the mean time to expulsion was longer in the oral group than the vaginal group.

In the study of Zhang et al,¹⁴ the 16% failure rate with misoprostol was greater than the 3% observed with surgical management. Hemorrhage and endometritis requiring hospitalization occurred in 1% or less of patients.

Christian et al¹⁵ stated that in early pregnancy there are few receptors and large doses of misoprostol may need to be given repeatedly in order to have an effect. With doses over 400 mcg, diarrhea can occur and some women patients experience a brief increase in temperature with shivering. Both effects are dose dependent and settle rapidly without

Discussion

In our study, we used 800 mcg vaginally and 600 mcg sublingually, both 6 hourly upto 3 doses and the mean dose required in vaginal group was 2044 mcg and in sublingual group was 1564 mcg, which was statistically significant ($P < 0.001$). However, the efficacy was similar in the two groups (88.89% in group-A, 92.85% in group-B) with comparable side effects. This is similar to the study of Tang et al⁶ who also had similar success rates of medical management in vaginal and sublingual groups (the dose used by the two routes was same) with no serious complications but the incidence of diarrhea and fatigue were significantly higher in the sublingual group. In our study also, fever/chills, vomiting were more in sublingual group.

Davis et al⁷ who in their study reported that complete expulsion without D&C occurred in 85% and of Shankar M, et al⁸ who observed complete medical evacuation 77.3% with a mean satisfaction of 66.7% with 800 mcg of misoprostol orally⁹ achieved success rate of 82% with 800 mcg of misoprostol vaginally as compared to 88.89% in our study while

Table 3 – Treatment outcome.

	Group-A		Group-B		Total	
	No.	%	No.	%	No.	%
Complete evacuation after 1 dose	2	3.70	1	1.79	3	2.73
Complete evacuation after 2 doses	19	35.19	20	35.71	39	35.45
Complete evacuation after 3 doses	27	50.0	31	55.35	58	52.72
No evacuation after 24 h – Surgical evacuation done (True drug failure)	6	11.11	4	7.14	10	9.09
Highly satisfied with the regime	27	50.00	28	50.00	55	50.00
Just satisfied with the regime	18	33.33	20	35.71	38	34.55
Unsatisfied with the regime	9	16.67	8	14.29	17	15.45
Dropout cases	5	4.20	4	3.36	9	7.56
1 Absconded	1	0.84	0	–	1	0.84
2 Surgical evacuation done for other causes	4	3.36	4	3.36	8	6.72
a Excessive hemorrhage	4	3.36	2	1.68	6	5.04
b Severe allergic reaction	0	–	1	0.84	1	0.84
c Time regimen not followed	0	–	1	0.84	1	0.84

Mean dose required in group-A = 2044 mcg, group-B = 1564 mcg, $P < 0.001$ HS. In others, P not significant.

Table 4 – Distribution of women patients according to side effects.

Side effects	Group-A		Group-B		Chi-square test
	No.	%	No.	%	P value LS
Cramping abdominal pain (severe)	15	27.78	18	32.14	0.085 at 1 DF; P = 0.77NS
Vomiting (severe)	2	3.70	6	10.71	1.099 at 1 DF; P = 0.295NS
Diarrhea (more than 4 episodes)	4	7.41	5	8.93	0.003 at 1 DF; P = 0.955NS
Fever/Chills	2	3.70	6	10.71	1.099 at 1 DF; P = 0.295NS
Headache	1	1.85	3	5.36	0.223 at 1 DF; P = 0.637NS
Dizziness	1	1.85	1	1.79	0.473 at 1 DF; P = 0.492NS
Allergic reaction	2	3.70	3	5.36	0.002 at 1; P = 0.967NS
P not significant.					

treatment. It is common to get lower abdominal pain due to the uterine contractions induced by misoprostol. Chawla et al¹⁶ applied 200 mcg misoprostol vaginally in the posterior fornix every 8 h to a maximum of five tablets. The procedure was successful in all cases. Two out of 30 cases required check curettage. Gastrointestinal side effects like vomiting and diarrhea were seen in few cases¹⁷ observed that the side effects, fever, nausea and vomiting more in the SL group, diarrhea and hot flushes more in the oral group. In our study also, fever/chills, vomiting were more in sublingual group.

Conclusion

Misoprostol is very effective in evacuation of the uterus in missed abortion, with the advantage of low cost, long shelf life, lack of need for refrigeration, easy availability and requires no surgery and hence no anesthesia. Thus, it may be advocated to be used in outpatient setting in the treatment of early pregnancy failure even at the primary care level. Our study showed that both regimes had comparable efficacy, acceptability (90%) and side effects. However, in women patients with less than six weeks period of gestation, the vaginal (800 mcg) route was distinctly superior whereas in women patients with 6–8 weeks the sublingual (600 mcg) route was more advantageous. For more than eight weeks period of gestation, any of the two routes may be used.

As the bioavailability varies with each route, the correct dose must be used for the route chosen e.g. sublingual, oral or vaginal. Routes should not be changed without checking the dose. The route of administration should be decided in accordance with the preference of the patient and the clinical situation.

Conflicts of interest

All authors have none to declare.

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