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EFFICACY, ACCEPTABILITY AND SAFETY OF MISOPROSTOL FOR THE TERMINATION OF EARLY PREGNANCY FAILURE

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ABSTRACT

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. To compare the efficacy ,side effects and acceptability of different regimes of misoprostol in causing expulsion of products of conception in early pregnancy failure. Women 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 tab. Misoprostol 600 mcg 6 hourly, sublingually for 3 doses. Success rate, complications, side effects and acceptability were the main outcome measures. All observations were noted and statistical analysed. Mean induction abortion interval 18.183 hrs. Women with less than six weeks gestational age had least mean induction-abortion interval time, 15.75$\pm$2.82 hrs in vaginal group but was highest in sublingual group 22$\pm$2hrs. ($p= 0.02$). Though after 8 weeks, both routes were equally effective. Mean dose required in group-A was 2044mcg and in group-B was 1564mcg($p< 0.001$). Efficacy of protocol 88.89% in group-A, 92.85% in group-B In both group, 50% women were found to be highly satisfied. Both regimes had comparable efficacy, acceptability(90%) and side effects. In women less than six weeks period of gestation, the vaginal(800mcg) route was distinctly superior, in women with 6-8 weeks the sublingual(600mcg) 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.

Key Words: Missed Abortion, Misoprostol, Acceptability, Side Effects, Early Pregnancy Failure.

INTRODUCTION

Early Pregnancy Failure represents a significant gynaecological 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. Besides risk of anaesthesia, which significantly increases the cost, it has been associated with 4-10% rate of early complication including infection, bleeding and less frequently injuries to cervix and uterine perforation along with long term complication of decreased fertility [2]. The use of prostaglandins, PGE2 vaginally replaced the surgical methods because besides being non-invasive, they had high success rate and patient acceptability [3]. However, the high expense of the medicine and instability in room temperature were barriers to their use in developing countries. Misoprostol-a synthetic prostaglandin E_1 analogue, available in tablet form, is cheap, stable at room temperature [4]. There is dearth of evidence to reveal satisfaction rate and safety profile among patients of oral and SL routes.

Aim of the Study

The aim of this study was to compare the acceptability and side effects of two regimes of misoprostol in causing the complete expulsion of products of conception in early pregnancy failure. The primary objective of study was measurements of acceptability and safety profile parameters (nausea, vomiting, diarrhea, hot flushes, and fever) of both the groups. The secondary objectives of the

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study were number of doses required for complete abortion, success rate and the induction to evacuation interval in both the groups

METHOD

This was a comparative, hospital based prospective study conducted from April 2012 to May 2013. Women 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 greater than 7 mm with no embryonic 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 foetal pole.

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 hours and minimum difference to be detected of 2 hours. Thus sample size came to be 50 patients in each group which was enhanced 55 assuming 10% dropout rate.

Group Allocation After counselling and informed written consent ,the women were divided into two groups using coin tossing method

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

Group B : In this group women 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 hours after 3rd dose of misoprostol , i.e. at 24 hours. If the uterus was was not felt empty on pervaginal examination or ultrasonography shows products of conception, then dilatation and evacuation was done and was considered a true drug failure. Side effects and patient's acceptability were recorded.

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

In the study, the mean age of women was 24.18 + 5.1 years. The efficacy in achieving complete abortion was 88.89% in group-A and 92.85% in group-B. This difference was not statically significant
(p= 0.695). Table 1.

The mean induction abortion interval (IAI) was 18.183 hrs, and it was not statistically different in the two groups. Duration of induction to evacuation interval of more than 24 hours was seen in 11.11% in group-A and 7.14% in group-B. These were the true drug failures and were surgically evacuated. Table 2.

Majority of women with missed abortion required three doses. Women with missed abortion who had required one dose were 3.70% in group-A and 1.79% in group-B. As the dose required in sublingual route was lower the mean dose required in group-A was 2044mcg and in group-B was 1564mcg and this was statically significance (p< 0.001).

Abdominal pain was seen in almost all cases but analgesia was required by only 27.78% in group-A and 32.14% in group-B. Other adverse effects were vomiting, diarrhea (more than 4 episodes) fever/chills and mild allergy. There was no statistical difference in the two groups. Table 3.

In both group, 50% women were found to be highly satisfied .Women were not satisfied due to either failure of treatment or side effect of misoprostol. Table 4.

Women were removed from study when the full dose could not be used 5 in goup A and 4 in group B. These were either due to excessive bleeding per vaginum or severe drug allergy or time of regime not followed. These were taken for surgical evacuation. Table 5.

On follow-up visit, most of cases had no complaints. Mild bleeding per vaginum, requiring no treatment and pain abdomen was reported for which analgesics was given. No women required evacuation on follow-up visit.

Table 1. Efficacy of the Two protocols

Efficacy of Abortion	Group-A		Group-B		Total		Chi Square Test
	No.	%	No.	%	No.	%	P value LS
Complete Abortion	48	88.89	52	92.857	100	90.90	0.154 at 1 DF; P = 0.695NS
True Drug Failure	6	11.11	4	7.1429	10	9.09	
Total	**54**	100.00	**56**	**110**	100		

Relative Risk = 0.957 (95% confidence interval: 0.850 to 1.078) Chi-square = 0.154 with 1 degree of freedom; P = 0.695

Table 2. Induction-Abortion Interval in the Two Groups

Induction-Abortion Interval (in hrs)	Group-A		Group-B		Total		Chi Square Test
	No.	%	No.	%	No.	%	P value LS
6 – 12	3	5.56	3	5.36	6	5.45	0.166 at 2 DF; P = 0.921 NS
12 – 18	28	51.85	27	48.21	55	50.00	
18 – 24	17	31.48	22	39.28	39	35.45	
More than 24 hrs	6	11.11	4	7.14	10	9.09	
Total	**54**	100.00	**56**	100.00	**110**	100.00	

Mean Induction –abortion interval (hrs) in Group-A=18.125, Group-B= 18.241 and overall= 18.183

Table 3. Dose Required

Doses	Group-A		Group-B		Total		Chi Square Test
	No.	%	No.	%	No.	%	P value LS
1	2	3.70	1	1.79	3	2.73	0.382 at 2 DF; P = 0.826 NS
2	19	35.19	20	35.71	39	35.45	
3	33	61.11	35	62.50	68	61.82	
Total	**54**	100.00	**56**	100.00	**110**	100.00	

Mean dose required in group-A=2044mcg, group-B=1564mcg, p<0.001**HS**

Table 4.Side Effects in the Two Groups

Side Effects	Group-A		Group-B		Chi Square Test
	No.	%	No.	%	P value LS
Severe Abdominal Pain	15	27.78	18	32.14	0.085 at 1 DF; P = 0.77 NS
Severe Vomiting	2	3.70	6	10.71	1.099 at 1 DF; P = 0.295NS
Diarrhoea (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 1DF; 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

Table 5. Level of Satisfaction/Acceptability in the two Groups

Level of Satisfaction	Group-A		Group-B		Total		Chi Square Test
	No.	%	No.	%	No.	%	P value LS
Highly Satisfied	27	50.00	28	50.00	55	50.00	0.146 AT 2 DF; P=0.930NS
Satisfied	18	33.33	20	35.71	38	34.55	
Unsatisfied	**9**	16.67	**8**	14.29	**17**	15.45	
Total	**54**	100	**56**	100.0	**110**	100	

Table 6. Dropouts

	Cause	Group-A	Group-B
1	Excessive Hemorrhage- Incomplete Abortion	4	2
2	Absconded	1	0
3	Allergic Reaction (severe)	0	1
4	Time regimen not followed	1	1

DISCUSSION

In our study, the two groups had comparable efficacy as mean induction abortion interval was similar. This is similar to the studies of Francisco Barcelo, Catalina De paco et al [5] who stated that total number of complete miscarriages after medical treatment 90.6% and 87.8% with 800 and 600 microgram respectively. In the study of Kushwah DS et al [6] complete abortion rate in sublingual group was 92% with an induction to evacuation interval of 5.6+_4.54hrs and 84% and induction to evacuation interval 9.445.61hrs in the oral group (p=.0002). Ngoc NT, Blum J, Westheimer E et al [7] used 800mcg Misoprostol oral or

vaginal Misoprostol single dose in missed abortion and reported mean induction abortion interval as 21hrs and 13hrs respectively.

Gronlund et al [8] used 400 mcg, single dose vaginally and found efficacy to be 71%whereas Ramsey et al [9] used 400 mcg/4 hourly upto 5 doses also vaginally, efficacy increased to 95% but side effects increased with fever in 67%.Graziosi et al [10] used 800 mcg/day for 2 doses vaginally, but with this time schedule had a efficacy of only 60% with 47% having retained products. When Ayres et al [11] used 600 mcg/ 4 hourly only 2 doses vaginally 57% efficacy was seen with 14% retained placenta and 6% diarrhea.

As the dose required in sublingual route was lower, 600 microgram as compared to 800 in vaginal route, the mean dose required in group-A was 2044mcg and in group-B was 1564mcg and this was statistically significant ($p< 0.001$).

Kushwah DS et al [6] studied mifepristone 200mg followed by doses (600mcg/dose). They required; sublingual group one (86%), two (4%), three (0%) and four (10%) and oral group one (62%), two (10%), three (10%) and four (18%) respectively.

In our study , there was no difference in the side effects in the vaginal and sublingual group. Kushwah DS et al in their study found that though the incidence of side effects- nausea (2%), diarrhea (10%) was same in the sublingual and oral groups, vomiting (6%) , fever (8%) was seen only in oral group. Ayres-de-Campos D et al [11] reported (94.6%) experienced abdominal pain, 73 (96.6%) vaginal bleeding, 10 (13.5%) nausea, 4 (5.4%) vomiting, 5 (6.8%) diarrhea, and 4 (5.4%) transient hyperthermia.

In our study, there was, no significance difference ($p= 0.930$) in satisfaction and acceptability in women in the two groups, Thus, either regimen can be given as women's choice. Kushwah DS et al reported that SL route had fewer undesirable effects, was more satisfactory, required less number of doses and so was more acceptable to the patient compared to the oral route and in their study, 92% women were satisfied with sublingual regimen as compared to only 72% women in oral group. Demetroulis et al [12] found 82.5% patients in the study group who had successful treatment expressed satisfaction, whereas only 58% of the surgical group did so. Wood SL et al [13] stated that patient satisfaction with misoprostol treatment was high with 19 of 21 participants reporting they would try medical management again if they experienced another missed abortion.

Tang OS, Lau WN et al [14] found the incidence of diarrhea was higher in the sublingual (70%) than the vaginal route (27.5%) ($p<0.005$). Other side effects were similar in each group, although fatigue was experienced by more women in the sublingual group than in the vaginal group (65 versus 40% : $P=0.043$). The overall acceptability of medical management was good. Most women said they would choose the medical method if they were allowed to choose again and would recommend the method to others. In the study of Shankar M, Economides DL, Sabin CA et al [15] 66.7% said that they would choose to have medical evacuation in a future miscarriage, while seven (9.3%) were unsure.

CONCLUSION

Both regimes had comparable efficacy, acceptability (90%) and side effects. In women less than six weeks period of gestation, the vaginal (800mcg) route was distinctly superior, in women with 6-8 weeks the sublingual (600mcg) 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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