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Original Research Article

Comparison of efficacy of 600 and 800 micrograms vaginal misoprostol in early pregnancy failure in SMGS: a tertiary health care hospital in Jammu, India

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ABSTRACT

Background: Misoprostol use in early pregnancy failure is varied and dose is not well established. Aim of this study was to compare efficacy and side effects of 600 versus 800 micrograms vaginal misoprostol in early pregnancy failure.
Methods: A randomized prospective observational study was conducted in the postgraduate department of obstetrics and gynaecology, SMGS hospital Jammu from November 2018 to October 2019 after getting approval from the ethical committee. Hundred patients (50 in group A and 50 in group B) admitted in labour room before 12 weeks of gestation with an ultrasound diagnosis of early fetal demise (missed abortion or brightened ovum) were treated medically with different doses of vaginal misoprostol.
Results: The success rate in patients in group A is 72% and group B is 88%, p=0.045 (difference is statistically significant). Patients who required suction and evacuation were 28% in group A and 12% in group B.
Conclusions: Use of misoprostol for medical management of 1st trimester missed/anembryonic is an effective, cheap, safe and convenient alternative to surgical evacuation. It was concluded that 800 micrograms vaginal misoprostol is more effective than 600 micrograms vaginal misoprostol. But 800 micrograms misoprostol has more side effects than 600 micrograms vaginal misoprostol.

Keywords: Misoprostol, Missed abortion, Early pregnancy failure

INTRODUCTION

Miscarriages are classified into early pregnancy losses (upto 12 weeks of conception) and late pregnancy losses (from 12th to 22nd week of gestation). Approximately 1 in 4 women will experience a miscarriage during her life time.[1] An increasing proportion of these unsuccessful pregnancies are now diagnosed on routine first trimester ultrasound scanning and designated as missed abortion, which account for approximately 10% of all first trimester miscarriages.[2] The standard treatment of both spontaneous and missed abortion used to be surgical evacuation of the uterus but expectant management or medical treatment are becoming reasonable alternatives.[3,4] The first agent used for medical abortion was mifepristone [5] initially approved in France in 1988. Misoprostol is a prostaglandin E1 analogue that has been initially used in the prevention of gastric ulcer disease.[6] In addition, misoprostol has been investigated as an agent to induce abortion.[7,8] Misoprostol causes cervical ripening. It has been proposed that this action appears to be mainly on the connective tissue stroma with evidence of disintegration and dissolution of collagen.[9] Misoprostol-a synthetic PGE1 analogue, is cheap, stable at room temperature and effective in inducing cervical ripening and uterine contractions. The most suitable dose of misoprostol for missed abortion is not yet clear. A single dose of 800 mcg of misoprostol by vaginal or oral route was recommended by national institute for health and care excellence.[10] However, some studies reported a converse opinion, by pointing out that a lower dose or different route may be equally effective.[11,12]

The objective of this study is to compare efficacy of 600 and 800 micrograms vaginal misoprostol in early pregnancy failure.

METHODS

The present study is randomized prospective observational study was conducted in the postgraduate department of obstetrics and gynaecology, SMGS hospital Jammu from November 2018 to October 2019 after getting approval from the ethical committee. A total of 100 patients admitted in labour room with ultrasound diagnosis of early fetal demise (missed abortion or blightened ovum) were included in the study. Patients in group A were given three doses of 600 micrograms vaginal misoprostol 6 hourly and the other 50 were given three doses of 800 micrograms vaginal misoprostol 6 hourly. Evaluation was done 6 hours after the 3rd dose of misoprostol i.e., at 24 hours. If the uterus was felt empty of products on vaginal examination or ultrasonography showed no products of conception, it was considered as treatment success.

RESULTS

The mean age of patients in group A is 26.2 and in group B is 25.92 years. Primigravida patients in group A were 32% (16) and in group B were 46% (23). Patients with one previous vaginal delivery (G2) were 26% (13) in group A and 22% (11) in group B. Patients with 2 or more previous vaginal deliveries were 42% (21) in group A and 32% (16) in group B. Mean haemoglobin level of patients in group A was 9.46 gm/dl and in group B was 9.20 gm/dl (Table 1). All these parameters were not statistically significant.

Table 1: Demographic data of the patients.

Variables	Group A-600 mcg	Group B-800 mcg
Maternal age (years)	26.2	25.92
Primigravida (%)	32 (16)	46 (23)
G2 (1 previous vaginal delivery) (%)	26 (13)	22 (11)
G3 or more (2 or more previous vaginal deliveries) (%)	42 (21)	32 (16)
Haemoglobin level, (g/dl)	9.46	9.20

Mean induction abortion interval was 15.17±4.96 hours in group A and 12.75±4.12 hours in group B. The difference was statistically significant (p=0.002). Induction abortion interval of patients with gestation age 6-8 weeks in group A was 15.08±4.92 hours and in group B was 13.29±3.78 hours. Induction-abortion interval of patients with gestation age 8-10 weeks in group A was 14.38±5.04 hours and in group B was 11.63±4.09 hours. Induction-abortion interval of patients with gestation age 10-12 weeks was 16.05±4.92 hours and in group B was 13.33±4.42 hours. Thus, in all gestation age groups, patients who received 800 mcg misoprostol (group B) had shorter induction-abortion interval compared to patients who received 600 mcg vaginal (group B) (Table 2).

Table 2: Gestation age and mean induction-abortion interval.

Gestational age (Weeks)	Induction abortion interval, group A-600 mcg, (Mean±SD) (Hours)	Induction abortion interval, group B-800 mcg, (Mean ± SD) (Hours)	P value
6-8	15.08±4.92	13.29±3.78	0.044 (S)
8-10	14.38±5.04	11.63±4.09	0.003 (S)
10-12	16.05±4.92	13.33±4.42	0.004 (S)
Overall	15.17±4.96	12.75±4.12	0.002 (S)

The induction-abortion interval decreased with increasing parity. In women with gestation age between 6-8 weeks the induction-abortion interval in group A was 16.54 hours for primigravida, 15.50 hours for second gravida and 13.20 hours for third gravida or more and in group B was 13.90 hours for primigravida, 13.58 hours for second gravida and 12.40 hours for third gravida or more. In women with gestation age between 8-10 weeks the induction-abortion interval in group A was 18.64 hours in primigravida, 13.50 hours in second gravida and 11 hours for third gravida or more and in group B was 14.50 hours for primigravida, 10.8 hours for second gravida and 9.6 hours for third gravida or more. In women with gestation age 10-12 weeks the induction-abortion interval in group A was 20.82 hours for primigravida, 14.33 hours in second gravida and 13 hours for third gravida or more and in group B was 16 hours for primigravida, 14 hours for second gravida and 10 hours for gravida 3 or more (Table 3).

Table 3: Gravidity and gestation age and induction abortion interval.

Gestational age (weeks)	Induction abortion interval, group A-misoprostol 600 mcg, (Hours)			Induction abortion interval, group B-misoprostol 800 mcg, (Hours)		
	Primigravida	G2	G3 and more	Primigravida	G2	G3 and more
6-8	16.54	15.50	13.20	13.90	13.58	12.4
8-10	18.64	13.50	11	14.50	10.8	9.6
10-12	20.82	14.33	13	16	14	10

USG was performed 6 hours after 3rd dose. No RPOCs were found in 34% patients in group A and 52% patients in group B. 1-5cc RPOCs were found in 36% patients in group A and 20% patients in group B. 5-10 cc RPOCs were found in 2 % patients in group A 8% patients in group B. >10cc RPOCs were found in 28% patients in group A and 20% patients in group B. Hence, greater number of patients in group A had more RPOCs than group B (Table 4).

Table 4: USG after 6 hours of 3rd dose.

USG after 6 hrs of 3rd dose (CC)	No. of patients in group A-600 mcg (%)	No. of patients in group B-800 mcg (%)	P value
No RPOCs	17 (34)	26 (52)	
1-5	18 (36)	10 (20)	0.0001 (S)
5-10	1 (2)	4 (8)	
>10	14 (28)	10 (20)	

The percentage of patients who required surgical evacuation after failed medical management was higher for group A (28%) than for group B (12%).

Success rate was higher in the 800 micrograms group as compare to 600 micrograms group. In patients with gestation age between 6-8 weeks the success rate in group A is 75% while in group B is 95.45%. In patients with gestation age between 8-10 weeks success rate is higher in group B i.e., 81.81% as compared to group A in which the success rate is 61.65%. Also, in the patients with gestation age between 10-12 weeks the success rate is lower for group A i.e., 76.64% than group B i.e., 83.33%. Hence, in all gestation groups 800 micrograms misoprostol is more effective than 600 micrograms misoprostol (Table 5). Also, the overall success rate is higher in group B i.e., 88% than in group A i.e., 72%.

Table 5: Success rate/gestational age.

Success rate/ gestational age (weeks)	Group A, no. of patients (%)	Group B, no. of patients (%)	P value
6-8	15 (75)	21 (95.45)	
8-10	8 (61.5)	18 (81.81)	0.023
10-12	13 (76.4)	5 (83.33)	

The occurrence of side effects was significantly higher with 800 micrograms misoprostol as compared to 600 micrograms misoprostol (Table 6). Excessive bleeding was noticed in 4 patients (8%) in group A and no such case was reported in group B. Nausea and vomiting occurred in 2 % patients in group A and in 4% in group B. Pain and cramps was reported in 6% patients in group A and in18% patients in group B. In our study fever and shivering occurred in 6% patients in group A and 14 % patients in group B.

Table 6. Side effects.

Side effects	Group A (600 mcg), no. of patients (%)	Group B (800 mcg), no. of patients (%)	P value
No side effect	39 (78)	32 (64)	
Excessive bleeding	4 (8)	0 (0)	0.001 (S)
Nausea	1 (2)	2 (4)	
Pain and cramps	3 (6)	9 (18)	
Fever and shivering	3 (6)	7(14)	

The patients were followed up after 1 week (Table 7). 78% patients in group A and 94% patients in group B reported no bleeding per vaginum at the end of 1 week. More patients in group A i.e., 22% reported spotting as compared to group B in which only 6% patients reported spotting at the end of 1 week.

Table 7: Follow up after 1 week.

Follow up after 1 week	Group A (600 mcg), no. of patients (%)	Group B (800 mcg), no. of patients (%)	P value
No BPV	39 (78)	47 (94)	0.043 (S)
Spotting	11 (22)	3 (6)	

DISCUSSION

The induction abortion interval in patients with 6-8 weeks period of gestation in group A is 15.08±4.92 hours while in group B is shorter i.e., 13.29±3.78 hours. In patients with 8-10 weeks period of gestation the induction abortion interval in group A is 14.38±5.04 hours while it is shorter in group B i.e., 11.63±4.09 hours. In patients with 10-12 weeks period of gestation the induction abortion interval is 16.05± 4.92 hours and again it is shorter in group B i.e., 13.33±4.42 hours. Overall, the mean induction abortion interval in group A is 15.17±4.96 hours and in group B is 12.75±4.12 hours. The difference between the two groups is statistically significant, p=0.002. Similar result was found in the study of Srikhao et al in which the induction to abortion time was shorter in the higher dosage group.[13] The mean time to abortion was significantly shorter in the 800 micrograms group than in the 400 micrograms group, 9 hours and 16 hours respectively with a p=0.01. The difference in their study was statistically significant. The induction abortion intervals were least for patients with 8-10 weeks period of gestation, higher for patients in 6-8 weeks period of gestation and maximum for patients with 10-12 weeks period of gestation in both the groups as mentioned above. These findings do not match with the study done by Hooja et al in which the induction abortion interval decreased with increasing gestation period.[14] In this study tablet misoprostol 800 micrograms were given 6 hourly for three doses. The induction abortion interval for patients with gestation ages 6-8 weeks, 8-10 weeks and 10-

12 weeks was 18.84±2.37 hours, 18.18±3.94 hours and 16.67±3.26 hours respectively.

The cases in the study groups were analysed according to the relation between parity and induction abortion interval. In women with gestation age between 6-8 weeks the induction abortion interval in group A was 16.54 hours for primigravida, 15.50 hours for second gravida and 13.20 hours for third gravida or more and in group B was 13.90 hours for primigravida ,13.58 hours for second gravida and 12.40 hours for third gravida or more. In women with gestation age between 8-10 weeks the induction abortion interval in group A was 18.64 hours in primigravida, 13.50 hours in second gravida and 11 hours for third gravida or more and in group B was 14.50 hours for primigravida, 10.8 hours for second gravida and 9.6 hours for gravida third or more. In women with gestation age between 10-12 weeks the induction abortion interval in group A was 20.82 hours for primigravida, 14.33 hours for second gravida and 13 hours for gravida third or more and in group B was 16 hours for primigravida, 14 hours for second gravida and 10 hours for third gravida or more. In both the groups it can be seen that the induction abortion interval decreases with increasing gravidity. The results are similar to the study of Anita et al, conducted on 200 patients with missed abortion up to 12 weeks period of gestation, in which the induction abortion interval decreased with increasing parity.[15]

USG was performed after 6 hours of 3rd dose. No RPOCs were found in 34% patients in group A and 52% patients in group B. 1-5cc RPOCs were found in 36% patients in group A and 20% patients in group B. 5-10 cc RPOCs were found in 2 % patients in group A and 8% patients in group B. >10 cc RPOCs were found in 28% patients in group A and 20% patients in group B. Hence, greater number of patients in group A had more RPOCs than group B. 4 patients in group A had excessive bleeding within 24 hours and an emergency suction evacuation was performed. These patients had large amount of RPOCs on per vaginum examination and S and E was performed immediately during the episode of excessive bleeding, thus they are included in the >10 cc RPOCs group. No similar study which included the amount of RPOCs could be found.

The percentage of patients who required surgical evacuation after failed medical treatment is higher for group A i.e., 28% than for group B i.e., 12%. The results are similar to the study of Barcelo et al in which the percentage of women who underwent surgical evacuation after failed medical treatment is higher in 600 micrograms misoprostol group i.e., 12.2% than in 800 micrograms misoprostol group i.e., 9.4%.[16]

Patients of all gestation ages had higher success rate in the 800 micrograms group as compared to 600 micrograms group. In patients with gestation age between 6-8 weeks the success rate in group A is 75% while in group B is 95.45%. In patients with gestation age between 8-10 weeks again the success rate is higher in the group B i.e., 81.81% as compared to group A in which the success rate is 61.65%. Also, in patients with gestation age between 10-12 weeks the success rate is lower for group A i.e., 76.64% than group B i.e., 83.33%. Hence it can be seen that in all gestation groups 800 micrograms misoprostol is more effective than 600 micrograms. The difference is statistically significant with a p=0.023. This result is similar to the study of Barcelo et al who used 600 and 800 micrograms vaginal misoprostol intravaginally in 946 women with missed miscarriage <12 weeks and found that the rate of complete evacuation in 600 micrograms group was 87.8% which was less than total rate of complete evacuation in 800 micrograms group which was 90.6%.[16]

The overall all success in group A is 72% which is less than the overall success rate in group B which is 88%. This result is comparable to the study of Kovavisarach et al in which 114 women were randomly assigned into 2 groups of equal sizes and the effectiveness of 600 and 800 micrograms misoprostol intravaginally were compared.[17] The rate of complete abortion within 24 hours was significantly higher in the group that received 800 mcg of misoprostol (68.4%) than in the 600 micrograms of misoprostol group (45.6%).

The occurrence of side effects was significantly higher with 800 micrograms misoprostol as compared to 600 micrograms misoprostol. Excessive bleeding was noticed in 4 patients (8%) in group A and no such case was reported in group B. This is similar to the study of Ayres de Campos et al which reported one such case (1.35%) of heavy vaginal bleeding requiring emergency surgical evacuation amongst patients who received 600 micrograms vaginal misoprostol for missed abortion.[18] Nausea and vomiting occurred in 2 % patients in group A and in 4% in group B. The results are consistent with the study conducted by Thakur et al in which nausea and vomiting was higher in the 800 micrograms group i.e., 26.25% as compared to 600 micrograms misoprostol group i.e., 5%. Pain and cramps were reported in 6% patients in group A and in 18% patients in group B. Nearly similar results were found in the study of Thakur et al in which 10% patients in 600 micrograms group had pain and cramps as compared to 50% women in 800 micrograms misoprostol group thereby meaning that patients taking higher dose of misoprostol suffered from more pain and abdominal cramps. Fever and shivering occurred in 6% patients in group A and 14 % patients in group B. Results are similar to the study of Thakur et al in which fever and shivering were higher in 800 micrograms group (48.75%) as compared to 600 micrograms group (12.5%).[19]

The patients were followed up after 1 week. 78% patients in group A and 94% patients in group B reported no bleeding per vaginum at the end of 1 week. More patients in group A i.e., 22% reported spotting as compared to group B in which only 6% patients reported spotting at the end of 1 week. Thus, total complete abortion rate is higher in group B as compared to group A. This is comparable to the result of Barcelo et al in which at the first follow up which was 1 week after treatment the total rate of complete

miscarriage was 90.6% in the 800-mcg group as compared to the 600-mcg group in which it was 87.8%.[16]

Limitations

The limitation of the study was the small sample size of the patients and lack of studies comparing the efficacy of 600 and 800 micrograms vaginal misoprostol in early pregnancy failure. Several additional and large randomized clinical studies are still required for most effective dose regimen of misoprostol for medical management of 1st trimester missed abortions.

CONCLUSION

The use of misoprostol for medical management of 1st trimester missed/anembryonic abortion is an effective, cheap, safe and convenient alternative to surgical evacuation. It is also concluded that 800 micrograms vaginal misoprostol is more effective than 600 micrograms vaginal misoprostol. But 800 micrograms misoprostol has more side effects than 600 micrograms misoprostol.

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