International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Mirza R et al. Int J Reprod Contracept Obstet Gynecol. 2022 Feb;11(2):365-369
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20220034

Original Research Article

Comparative study of mifepristone followed by misoprostol with misoprostol alone for treatment of early pregnancy failure: an interventional randomised clinical study in a tertiary care hospital

Robina Mirza, Ankita Sharma, Pooja Sharma*

Department of Obstetrics and Gynaecology, SMGS, Jammu, Jammu and Kashmir, India

Received: 19 December 2021
Accepted: 04 January 2022

***Correspondence:**
Dr. Pooja Sharma,
E-mail: Pooja.polar1@gmail.com

ABSTRACT

Background: Early pregnancy failure (EPF) is a common experience for women. Medical management allows for expulsion of the nonviable pregnancy in a controlled manner without any surgical risk. The aim of this study was to compare efficacy and safety of mifepristone followed by misoprostol with misoprostol alone in management of EPF.
Methods: This was a prospective comparative interventional randomised clinical study conducted at Shri Maharaja Gulab Singh hospital, Jammu, Jammu and Kashmir India from November 2019 to October 2020. A total of 200 patients with gestational age less than 13 weeks and ultrasound diagnosis of EPF were included in the study and randomly divided into two groups, group A (100 patients) received tab. mifepristone 200 mg orally 24 hrs before the use of Tab misoprostol 800 ug per vaginally. If no expulsion occurs within 4 hours, repeat doses of 400 ug misoprostol were given per vaginally at 4-hourly interval to a maximum of 2 doses in women less than or equal to 9 weeks by ultrasound and 4 doses in women more than 9 weeks by ultrasound. Group B (100 patients) received only Tab misoprostol in similar doses without prior mifepristone. The study was performed after approval from the institutional ethical committee. The data was analysed using computer software Microsoft Excel, Statistical and IBM SPSS version 21.0. The statistical difference in mean value between two groups was tested using unpaired 't' test. The qualitative data was compared using Fischer's exact test.
Results: The success rate was higher in group A 92% than group B where it was 76%. The mean induction-abortion interval and dose of misoprostol required for expulsion were 6.56±.66 hrs in group A and 10.40±4.33 hrs in group B and 1126.88±536.06 ug in group A and 1583.33±364.58 ug in group B. The patients in group A experienced significantly less side effects than those in group B, 19% versus 32% and also required fewer blood transfusions than group B, 2% versus 5%.
Conclusions: In the present study we came to the conclusion that mifepristone followed by misoprostol is more effective, safe and acceptable than misoprostol alone.

Keywords EPF, Missed abortion, Mifepristone, Misoprostol

INTRODUCTION

Early pregnancy failure (EPF) is a distressing event for the woman, at the same time it contributes to high maternal morbidity and mortality in developing countries.

Early pregnancy loss is one of the most common complications of pregnancy, accounting for almost 50% of conceptions and 12-15% of all clinically diagnosed pregnancies.[1]

Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or foetus without foetal heart activity within the first 12 6/7 weeks of gestation.[2,3]

The combination of misoprostol and mifepristone is the current standard of care in the termination of a viable pregnancy in the first trimester, with success rates exceeding 95%.[4] Studies have shown promising results for utilization of this protocol in treatment of missed abortion.

The idea behind this combination use of drugs is that non-viable pregnancies contain viable trophoblast tissue, which produces hormones that make these pregnancies more susceptible to antihormone therapy and uterotonics.[5] Therefore, administering mifepristone prior to the application of misoprostol may enhance the success rate of non-surgical management.

METHODS

This prospective comparative interventional randomised clinical study was conducted at Shri Maharaja Gulab Singh hospital, Jammu, Jammu and Kashmir India over a period of one year i.e., November 2019 to October 2020.

A total of 200 patients were included in the study with an ultrasound diagnosed EPF and gestational age of less than 13 weeks. Those with incomplete abortion, inevitable abortion, known coagulopathy, haemodynamic instability, anaemia Hb<8 g%, known allergy to mifepristone/misoprostol or those showing signs of infection were excluded from the study.

The patients were randomly divided in two groups. Group A received tab mifepristone 200 mg orally on admission into the labour room, followed by 800 ug of Tab misoprostol per vaginally after 24 hrs. If no expulsion occurs within 4 h, repeat doses of 400 ug misoprostol were given per vaginally at 4-hourly interval to a maximum of 2 doses in women less than or equal to 9 weeks by ultrasound and 4 doses in women more than 9 weeks by ultrasound. Group B followed only the misoprostol doses in similar manner without prior mifepristone. Patient were discharged from hospital on the next day. Surgical evacuation was done if no bleeding occurred within 48 h of completion of protocol with scan suggestive of intact gestational sac or the patient had excessive bleeding anytime or at 2-week follow-up visit, if ultrasound was suggestive of intact gestational sac/endometrial thickness more than 15 mm. Need for performing surgical evacuation was considered treatment failure.

A written informed consent was taken from each patient for inclusion in the study with awareness regarding the risks and complications of the procedure. The patients who refused were excluded. The study was performed only after approval from the institutional ethical committee.

The data was analysed using computer software Microsoft excel, statistical and IBM SPSS version 21.0. Data was reported as mean±standard deviation and proportions as deemed appropriate for quantitative and qualitative variables respectively. The statistical difference in mean value between two groups was tested using unpaired 't' test. The qualitative data was compared using Fischer's exact test. A $p<0.05$ was considered statistically significant. All p values were two-tailed.

RESULTS

In our study the majority of patients were multigravida in both the groups, gravidity 3 and above constituted 43% and 39% in group A and group B respectively (Table 1).

Table 1: Distribution of patients according to gravidity.

Gravidity	Group A (no. of patients)	Group B (no. of patients)	P value
Primigravida	25	29	
G2	32	32	0.789
G3 and more	43	39	(N.S)
Total	100	100	

Patients in group A had a mean age of 27.54 years compared to 28.16 years in group B (Figure 1).

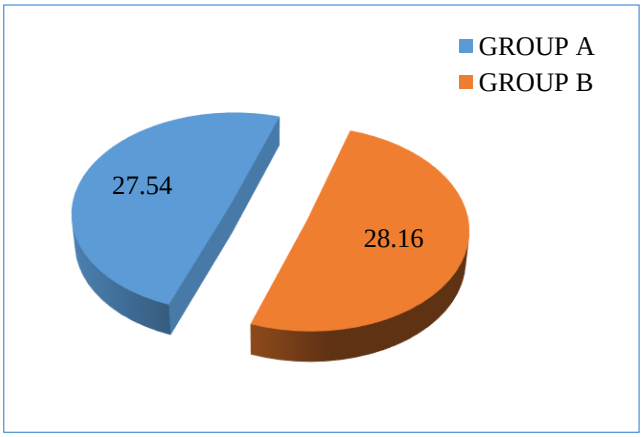

Figure 1: Mean age of the patients.

The mean haemoglobin of patients in group A was 10.47 g/dl and that of group B was 10.5 g/dl (Figure 2). There was no statistical difference with respect to gravidity, age and mean haemoglobin in both of the groups.

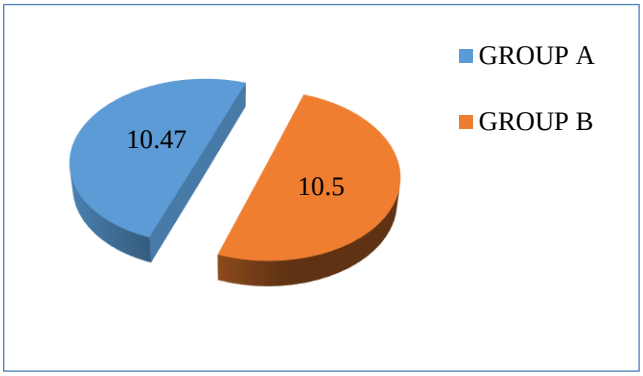

Figure 2: Mean Hb levels of the patients.

The mean induction abortion interval of patients belonging to in group A was 6.56±4.66 hrs and induction abortion interval of patients in group B was 10.40±4.33 hours. Table 2 depicts the time interval in both groups with respect to gestational age of the patients.

In group A, the mean dose of misoprostol required for expulsion of products of conception was 1126.88±536.06 ug. In group B the mean dose of misoprostol required for expulsion of products of conception was 1583.33±364.58 ug. The dose of misoprostol required with gestational age was varied as discussed in Table 3.

Table 2: Gestation wise mean induction abortion interval.

Gestational age (weeks)	Group A		Group B		P value
	No. of patients	Mean±SD (Hours)	No. of patients	Mean±SD (Hours)	
6 -9	59	5.03±3.03	49	8.47±2.92	0.0000 (S)
9-11	25	8.24±5.76	19	12.18±3.56	0.005 (S)
11-13	12	10.58±5.52	16	14.22±5.10	0.08 (N.S)
Overall	96	6.56±4.66	84	10.40±4.33	0.00001 (S)

Table 3: Gestational age wise average dose of misoprostol required.

Gestational age (weeks)	Group A		Group B		P value
	No. of patients	Mean dose of misoprostol (ug)	No. of patients	Mean dose of misoprostol (ug)	
6-9	59	1023.72±428.45	49	1346.93±254.22	0.0000 (S)
9-11	25	1200±632.46	19	1705.26±322.27	0.002 (S)
11-13	12	1466.66±667.47	16	1850±382.97	0.05 (N.S)
Overall	96	1126.88±536.06	84	1583.33±364.58	0.00000 (S)

In group A there were 81% of patients who showed no side effects. In group B the figure was 68%, side effect profile of both the groups are presented in Figure 3.

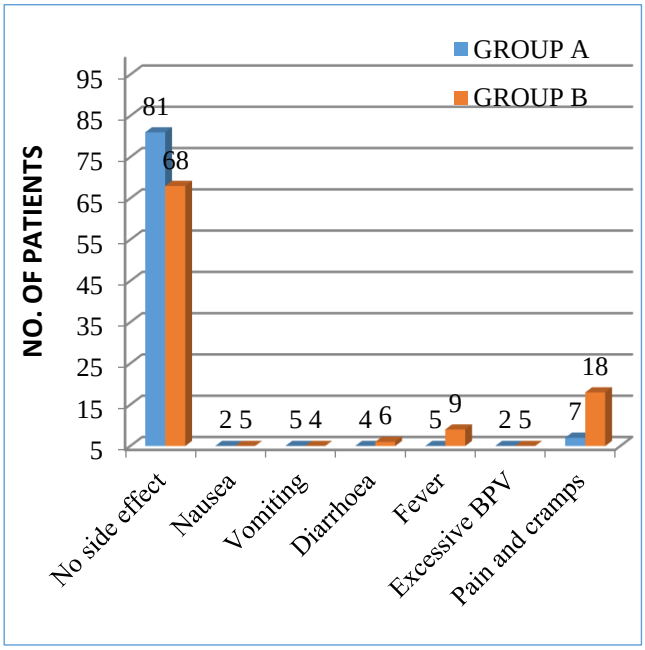

Figure 3: Multiple bar diagram of side effects.

In group A 8 patients required suction and evacuation to be performed. In group B there were 24 such patients. Therefore, the success rate in group A was 92% whereas it was 76% in group B (Table 4).

Table 4: Success rate in both the groups.

Variables	Group A (no. of patients)	Group B (no. of patients)	P value
Success	92	76	0.002 (S)
Failure	8	24	

The 88 patients out of 100 in group A were ready to opt for this method in future or recommend it to others for management of pregnancy failure. The 73 out of 100 in group B were satisfied with this method of management (Table 5).

Table 5: Patient acceptability (recommend/opt in future).

OPT/ recommend in future	Group A (no. of patients)	Group B (no. of patients)	P value
Yes	88	73	0.007 (S)
No	12	27	

DISCUSSION

In our study 25% patients in group A and 29% patients in group B were primigravida. Second gravida in both the group were 32%. 43% patients in group A and 39% patients in group B were third gravida or more. The difference in the number of patients according to gravidity is statistically insignificant (p=0.789). Creinin et al also

observed no statistically significant difference related to gravidity.[6]

The patients in group A had a mean age of 27.54 years compared to 28.16 in group B. This is similar to the study of Schreiber et al in which mean age was 30.7 and 30.2 in mifepristone pre-treatment group and misoprostol alone group respectively.[7]

There was no statistically significant difference between the haemoglobin levels in the two groups. The mean haemoglobin of patients in group A was 10.47 g/dl and that of group B was 10.5 g/dl. This is similar to the study of Sinha et al who observed no significant difference.[5]

The mean induction abortion interval of patients belonging to in group A was 6.56±4.66 hrs and 10.40±4.33 hrs in group B. The difference was statistically significant. This was similar to Sinha et al in which the mean induction to expulsion interval (4.74±2.24 vs. 8.03±2.77 hrs) was significantly less in the group I (mifepristone followed by misoprostol) as compared to group II (placebo followed by misoprostol).[5] There were 9 patients (9%) in group A who expelled within 24 hrs of mifepristone and didn't require misoprostol. Likewise, in study by Wagaarachchi et al there were 18.1% patients that expelled with mifepristone alone.[8] Also El-Refaey et al observed an expulsion rate of 13% with mifepristone alone.[9]

The cases in the study were analysed according to relationship between the dose of misoprostol required for expulsion of products and period of gestation. In 6-9 weeks, period of gestation the mean dose of misoprostol in group A was 1023.72±428.45 ug whereas in group B it was 1346.93±254.22 ug. In 9-11 weeks, period of gestation the mean dose of misoprostol in group A was 1200±632.46 ug and in group B it was 1705.26±322.27 ug. In 11-13 weeks, period of gestation the mean dose of misoprostol in group A was 1466.66±667.47 ug whereas in group B it was 1850±382.97 ug. Overall, in group A the mean dose of misoprostol required for expulsion of products of conception was 1126.88±536.06 ug. In group B the mean dose of misoprostol required for expulsion of products of conception was 1583.33±364.58 ug. A similar kind of relationship was acknowledged by Farzaneh et al while comparing the effect between two doses of vaginal misoprostol in the termination of first-trimester pregnancy, the mean gestational age of the two study groups were 8.78 weeks and 10.27 weeks and they required 1208.89 ug and 1506.76 ug of misoprostol respectively and dose increased with gestational age.[10]

It has also been seen in our study that overall side effects were seen less frequently in group A than group B. The most common side effect experienced were abdominal cramps and pain in 7% patients of group A and 18% patients of group B. These can be attributed to overall more dosage of misoprostol required in group B. Schreiber et al in his study noted that the most common side effect was fatigue and headache.[7] Nausea and vomiting were also frequently occurring side effects in both the groups seen in 37.6% and 26.8% patients in mifepristone pre-treatment group and 37.1% and 15.2% patients in misoprostol only group.

The success rate in this study was recorded as 92% in group A and 76% in group B. The success was more with combined used of mifepristone and misoprostol. Wagaarachchi et al observed a success rate of 84.1% while using mifepristone and misoprostol together for medically terminating first trimester missed abortion.[8] A success of 93% was reported by Schreiber et al in his study where he used both mifepristone and misoprostol for management of EPF.[11] A treatment success rate of 96.9% was reported by Creinin et al with combination of both these drugs for first trimester missed abortion.[6] Schreiber et al in his study found out a success rate 83.3% of in group pre-treated with mifepristone versus 67.1% in group receiving misoprostol alone.[7] Likewise, Chu et al reported success of 83% in mifepristone pre-treated group versus 76% in placebo pre-treated group.[12] This wide range of treatment success is attributed to different doses of these drugs like mifepristone (200-600 mg) and misoprostol (200-2400 ug) and different routes of misoprostol administration. There is also variation is the defining treatment success in various studies.

It has been observed in our study that the patients seemed to be well satisfied with this method of termination of pregnancy failure. This cohort comprised of 88% patients in group A and 73% patients in group B. The difference was statistically significant. Those who were not ready to choose this method in case of a repeat abortion in future or recommend it to their near and dear ones were the patients in whom these methods failed or those who experienced excessive side effects. This was similar to the study undertaken by Sinha et al where the overall procedure was more acceptable to patients in group I who received mifepristone prior to misoprostol induction rather than placebo.[5]

Limitations

The dose of Tab mifepristone used was only 200 mg, several studies use dose up to 600 mg. Misoprostol was used by vaginal route only. Its oral or sublingual use was not compared in the study.

CONCLUSION

The medical management of EPF is an effective, safe and cheap alternative to the surgical method. It is concluded that mifepristone followed by misoprostol is more effective, safe and acceptable than misoprostol alone.

I would also like to mention that several additional and large randomized clinical studies are still required for more effective dose regimen and combination of both these drugs; mifepristone and misoprostol for medical management of EPF.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Hemminki E. Treatment of miscarriage: current practice and rationale. Obstet gynecol. 1998;91:247-53.
2. American college of obstetricians and gynaecologists: Early Pregnancy Loss. Practice Bulletin No. 150, Reaffirmed 2017c. 2015.
3. National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. NICE Clinical Guideline 154. Manchester (UK): NICE. 2012.
4. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. BJOG. 2005;112(8):1102-08.
5. Sinha P, Suneja A, Guleria K, Aggarwal R, Vaid NB. Comparison of Mifepristone Followed by Misoprostol with Misoprostol Alone for Treatment of Early Pregnancy Failure: A Randomized Double-Blind Placebo-Controlled Trial. J Obstetr Gynecol India. 2018;68(1):39-44.
6. Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. Medical Abortion at the Same Time (MAST) Study Trial Group. Obstet Gynecol. 2007;109:885-94.
7. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT**.** Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med. 2018;378:2161-70.
8. Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Hum Reprod. 2001;16(9):1849-53.
9. El-Refaey H, Hinshaw K, Henshaw R, Smith N, Templeton A. Medical management of missed abortion and anembryonic pregnancy. Br Med J. 1992;305:1399.
10. Farzaneh F, Khosravi D, Hosseini MS, Defaei S, Fazel A. Comparison of the effect between two doses of vaginal misoprostol in the termination of first-trimester pregnancy: a double-blinded randomized trial. Obstet Gynecol Int J. 2018;9(1):00311.
11. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ. Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception. 2006;74(6):458-62.
12. Chu JJ, Devall AJ, Beeson LE, Hardy P, Cheed P, Sun Y et al. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (Mife Miso): a randomised, double-blind, placebo-controlled trial. Lancet Elsevier Ltd. 2020;396(10253):770-8.

Cite this article as: Mirza R, Sharma A, Sharma P. Comparative study of mifepristone followed by misoprostol with misoprostol alone for treatment of early pregnancy failure: an interventional randomised clinical study in a tertiary care hospital. Int J Reprod Contracept Obstet Gynecol 2022;11:365-9.