ORIGINAL RESEARCH

Comparison of Mifepristone followed by Misoprostol With Misoprostol Alone for Management of Early Pregnancy Failure: A Randomized Controlled Study

[1]Dr. Kanchan Dalmia, [2]Dr. Priya Jaiswal, [3]Dr. Madhuri Nair

[1]Professor & Head, [2,3] Post Graduate Student, Department of Obstetrics and Gynecology, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India

Corresponding Author
Dr. Madhuri Nair
Post Graduate Student, Department of Obstetrics and Gynecology, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India
Email: madhurinair3@gmail.com

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ABSTRACT

Introduction: The drugs commonly employed for the induction of abortion and the management of incomplete abortion or intrauterine foetal demise (IUFD) are typically a combination of mifepristone and misoprostol, or alternatively, misoprostol alone. The current study has been conducted with the aim of comparing theefficacyofmifepristonefollowedbymisoprostol with misoprostol alone for management of early pregnancy failure. **Methodology:** A Randomized controlled study was conducted in the department of Obstetrics and Gynaecology, Rohilkhand Medical College and Hospital, Bareilly from 1stNovember2019 to 31st October 2020. among 102 women having symptoms and signs suggestive of early pregnancy failure before 12weeks of gestation. Statistical analysis was done using SPSS software (version 23) and the result were calculated in percentage and compared using chisquare test. A p-value of less than 0.05 was considered significant. **Observations:** In the present study, in mifepristone followed by misoprostol group 86.27% patient had complete abortion where as among patients in misoprostol only group, 54.90%of them had complete abortion. In group A, merely 9.8% patients requiredblood transfusion whereas in group B, 29.41% patients needed blood transfusion. **Conclusion:** We conclude that the utilization of a combination of mifepristone and misoprostol for the medical management of early pregnancy failure is considered a safe and non-invasive alternative to surgical evacuation and is better than misoprostol alone. Consequently, patients experiencing early pregnancy failure are more likely to accept or tolerate the treatment.

Keywords: Earlypregnancy failure, Evacuation, Missed abortion, Mifepristone, Misoprostol

INTRODUCTION

One of the most frequent pregnancy complications is Early Pregnancy Failure (EPF) of less than 12 weeks, since half of the conceptions results in EPF. [1]Medical intervention is necessary for two primary categories of miscarriage: missed miscarriage (an-embryonic gestation and embryonic demise) and incomplete miscarriage. A blighted ovum results from an early disturbance of normal embryonic development. There are several management options available for early pregnancy failure, which include expectant management, surgical evacuation, and medical management.

The initial therapeutic approach for missed miscarriage involves expectant management, when women are advised to wait for a period of 7 to 14 days for spontaneous expulsion of the pregnancy tissue from the uterus. [2] If the expectant management approach proves to be ineffective or is not deemed suitable by the mother, medical treatment is the preferred alternative. The efficacy of expectant treatment for early pregnancy failure is insufficient to warrant its frequent implementation in clinical settings. The time duration necessary for total expulsion to transpire exhibits variability in cases of expectant management, hence giving rise to significant uncertainty regarding the timing of complete evacuation. Therefore, it is necessary to conduct extended periods of follow-up as well. [3]

The medical management approach facilitates the removal of retained pregnancy tissue by the administration of pharmaceutical agents. Medical

management is a widely favoured approach among women and is endorsed in clinical recommendations of worldwide significance. [3,4,5]

For a considerable period of time, surgical evacuation has been widely employed as the prevailing method. However, this approach is associated with potential hazards such as anesthesia-related complications, uterine perforation, intrauterine adhesions, cervical trauma, infections that may result in infertility, pelvic pain, and an elevated likelihood of ectopic pregnancy. [6] Additionally, there are elevated expenses associated with hospitalisation and surgical interventions. [7] Given the potential consequences in both the short and long-term following surgical intervention, the significance of medical management is paramount. [8]

Non-viable pregnancies are characterized by the presence of viable trophoblastic tissue, which secretes hormones that render these pregnancies more sensitive to antihormone therapy and uterotonics. According to this theoretical framework, multiple pharmaceutical substances (including mifepristone, misoprostol, gemeprost, dinoprost, and methotrexate) were employed in numerous research investigations to address the management of EPF. These medications were administered using diverse dosage regimens and modes of administration across different studies.[9]The drugs commonly employed for the induction of abortion and the management of incomplete abortion or intrauterine foetal demise (IUFD) are typically a combination of mifepristone and misoprostol, or alternatively, misoprostol alone.

Mifepristone functions as an anti-progestin by selectively binding to progesterone receptors, so impeding the activity of progesterone and thereby disrupting the progression of pregnancy.Misoprostol is a synthetic counterpart of prostaglandin E1, which can be administered in conjunction with mifepristone or as a standalone treatment.

Misoprostol possesses a diverse array of uses in the field of reproductive health, encompassing the induction of labour, the management of both spontaneous and induced abortion, as well as the prevention and treatment of postpartum haemorrhage. The utilisation of misoprostol in abortion therapy, whether in conjunction with mifepristone or as a standalone treatment, presents numerous benefits due to its convenient handling and storage, non-invasive nature, and established cost-effectiveness.

Mifepristone exhibits oral bioavailability of merely 25%. The half-life of the compound ranges from 20 to 36 hours. It is suitable for the termination of pregnancy within the first seven weeks. A single oral dose of 600 mg has been observed to induce complete abortion in approximately 60-85% of cases. In order to enhance the rate of success, the current recommendation entails administering a single oral dosage of 400 mg of misoprostol 48 hours after the initial intervention. This method has been found to produce a success rate over 90% and is widely recognised as the preferred non-surgical approach for performing abortions during the initialphase of the first trimester. This treatment is typically considered to be safe; however, certain situations may present complications such as prolonged bleeding and unsuccessful abortion. Additional adverse effects include anorexia, nausea, fatigue, abdominal discomfort, uterine cramps, and diarrhoea. Other applications encompass cervical ripening, postcoital contraception, monthly contraceptive administration, labour induction, and the management of Cushing's syndrome.Nevertheless, the application of mifepristone in the medical termination of early pregnancy failure (EPF) lacks a solid foundation, as research has produced conflicting findings about the effectiveness of mifepristone as a pre-treatment prior to misoprostol administration. This issue requires further investigation and resolution. The efficacy of therapy protocols utilising a combination of mifepristone and prostaglandins analogues for the management of early pregnancy failure has been investigated, revealing success rates ranging from 52% to 84%. [11]

Previous research has yielded inconsistent findings about the potential advantages of including mifepristone alongside misoprostol. Furthermore, the quantification of blood loss has not been undertaken in prior investigations. Therefore, the current studyhas been conducted with the aim of comparing theefficacyofmifepristonefollowedbymisoprostolwith misoprostol alone for managementof earlypregnancy failure by estimating the proportion of complete evacuation of the conceptus and by assessing the amountofvaginalblood lossamong thetwogroups.

METHODOLOGY

Type of Study: Randomized controlled study.

Place of Study: This study was conducted in the department of Obstetrics and Gynaecology, Rohilkhand Medical College and Hospital, Bareilly.

Study Duration: One year (1stNovember2019 to 31stOctober 2020)

Ethical approval: Necessary ethical approval was obtained from the Institutional Ethical Committee (IEC), Rohilkhand Medical College and Hospital, Bareilly, with IEC number IEC/44/2019/SEPT.

Sample Size: Sample size was calculated assuming the baseline success rate of57.8% in misoprostol group and expecting an increase in success rate to 88.7% in mifepristone plus misoprostol group. A trial with a power of 90% and an alpha value of 0.05 yielded a required minimum sample of 102 women (by using PS-2 software), i.e., 51 in eachgroup.

Sampling frame: All patients having symptoms and signs suggestive of early pregnancy failure before 12weeks of gestation.

INCLUSION CRITERIA

- Patients willing to participate and ready for follow up.

- Hemodynamically stable patients.
- Patients with missed abortio n with gestational age <12weeks.
- Patients with blighte dovum.

EXCLUSION CRITERIA

- Pregnancywithgestationalage>12weeks.
- Patientswith ectopicpregnancy.
- Patientwithincompleteabortion.
- Contraindicationtomifepristone(chroniccorticosteroidadministration) and misoprostol(asthma,hypertension,glaucoma,mitralstenosis)
- Cardiovasculardisease(angina,valvulardisease)
- Haemoglobin<10gm/dl
- Breastfeeding

PROCEDURE

All patients having symptoms and signs suggestive of early pregnancy failure before 12weeks of gestation were subjected to transvaginal ultrasonography(TVS). Those patients who were diagnosed as having early pregnancy failure in the form of either blight edovumormissed abortion were counseled about all the options available for management of early pregnancy failurewiththeiradvantagesanddisadvantages. Those patients who opted for andfulfill the inclusion and exclusion criteria for the medical management wereincludedin thestudy.

Detailed history with thorough general, systemic and obstetrical examination was done and documented in a pre-design proforma. Patients were subjected to investigations such as haemoglobin concentration, Blood group, random blood sugar, Serum thyroid stimulating hormone, viral markers, VDRL, Urineroutineandmicroscopy,Husband'sbloodgroupwasdoneinthosepatientswhoturnoutto be Rh negative. Patients were allotted to group A and group B by computergeneratedrandomization.

GROUP A comprised of patients who were given 200mg of mifepristone orally followed by 800 micrograms of misoprostol per vaginally after 36 hours. If no expulsion occurs in 6hours, then repeat dose of 400microgram of misoprostol pervaginally was given four hourly to a maximum of two doses.

GROUP B patients were given 800 micrograms of misoprostol per virginally, if no expulsion occurs in 6hours, then repeat dose of 400microgram of misoprostol pervaginally was given four hourly to amaximum of two doses.

After 24 hours of last dose of misoprostol patients were subjected to hemoglobin estimation and a transvaginal ultrasound to ruleoutany retained products of conception. Patients showing retained products of conception in either group were subjected to surgical evacuation. The number of patients showing complete evacuation in either group was noted, vaginal blood loss was also noted for each patient and need of blood transfusion in any patient was recorded. All patients were advised to come after one week for followup. They were enquired and examined for any persistent bleeding, pain, signs of infection. Any complications if detected were managed accordingly.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software (version 23) and the result were calculated in percentage and compared using chisquare test. A p-value of less than 0.05 was considered significant.

OBSERVATIONS

To study the effect of Mifepristone plusMisoprostol and Misoprostol alone on early pregnancy failure, 102 patients were randomized into two groups. Group A was subjected to Mifepristone plusMisoprostol while Group B was subjected to Misoprostol alone.

Table1: Distribution of patients based on age (N=102)]

Variables		GROUPA N=51	GROUPB N=51	Chi square (p-value)
Age(Years)	20-25	12 (23.53)	10 (19.61)	1.172 (0.556)
	26-30	26 (50.98)	23 (45.10)	
	31-35	13 (25.49)	18 (35.29)	
	Mean ±SD	28.68 ±3.79	27.78 ±3.44	—

[Frequency (percentage)]

In**groupA**,about half of them(50.98%)wereintheagegroup26-30yearsfollowedby in 31-35 years of age group (25.49%)witha mean age of 28.68 years. In **group B**, majority of the patients (45.10%) were in the age group 26-30 years followed by in 31-35 years ofagegroup (35.29 %) with a meanageof27.78 years. However, the difference in the age distribution among the two groups was not statistically significant making the two groups comparable for further analysis. [Table 1]

Table2: Distribution of patients based on Obstetric characteristics (N=102)]

Variables		GROUP A N=51	GROUP B N=51	Chi-square (p-value)
Gravida	Primigravida	3 (5.88)	2 (3.92)	0.788 (0.940)
	Gravida2	8 (15.69)	5 (9.80)	

	Gravida3	23 (45.10)	24 (47.06)	
	Gravida4	14 (27.45)	14 (27.45)	
	Gravida5 or more	3 (5.88)	6 (11.76)	
Parity	Nullipara	3 (5.88)	2 (3.92)	0.596 (0.963)
	Para 1	15 (29.41)	11 (21.57)	
	Para 2	20 (39.22)	24 (47.06)	
	Para 3	10 (19.61)	12 (23.53)	
	Para 4 or more	3 (5.88)	2 (3.92)	
Gestationalage	<6weeks (<42days)	14 (27.45)	18 (35.29)	0.729 (0.393)
	6-12 weeks (42-84days)	37 (72.55)	33 (64.71)	

[Frequency (percentage)]

In **group A**, majority(45.10%) of the patients were Gravida 3 followed by Gravida 4 (27.45%). **GroupB** shows similar distribution with maximum(47.06%) patients ofGravida3followedbyGravida 4 (27.45%). Considering parity, in **group A**, majority(39.22%) of the patients were Para 2, similarly, In **group B**, maximum (47.06%) patients were Para 2. Gestational age of the patients was assessed and found that in **group A**, about three-quarters (72.55%) patient had gestational age between 6-12weeks in comparison to **group B**, 64.71% patient had gestational age between 6-12 weeks. [Table 2]

Table 3: Distribution of patients according to the requirement of repetition of misoprostol dose(N=102)

Variables	GROUPA N=51	GROUPB N=51	Chi-square (p-value)
No Repetition	35 (68.63)	11 (21.57)	23.95 (<0.001)
Single Repetition	10 (19.61)	18 (35.29)	
Two Repetition	6 (11.76)	22 (43.14)	

[Frequency (percentage)]

In **group A**, more than two-third(68.63%)of patients did not require misoprostol repetition while 11.76% patients required two repeatdoses of misoprostol. **In group B**, less than one-fourth (21.57%) patients did not required misoprostol repetition whilesignificantly higher proportion(43.14%) of patients required two repeat doses of misoprostol as compared to group A. [Table 3]

Table4: Distribution of patients based on the outcome, the need for surgical evacuation, vaginal blood lossand need for blood transfusion(N=102)

Variables		GROUPA N=51	GROUPB N=51	Chi-square (p-value)
Outcome	CompleteAbortion	44 (86.27)	28 (54.90)	12.08 (<0.001)
	IncompleteAbortion	4 (7.84)	13 (25.49)	
	PersistentGestationalSac	3 (5.88)	10 (19.61)	
SurgicalEvacuation	Required	7 (13.73)	23 (45.10)	12.089 (<0.001)
	Not required	43 (86.27)	28(54.90)	
Blood Loss (Fall in Hb in gm/dl)	< 1.5 gm	40 (78.43)	31 (60.78)	2.467 (0.481)
	1.5- 3.0 gm	8 (15.69)	15 (29.41)	
	3.1- 4.5 gm	2 (3.92)	3 (5.88)	
	>4.5 gm	1 (1.96)	2 (3.92)	
Need forblood Transfusion	Required	5 (9.80)	15 (29.41)	6.22 (0.012)
	Not required	46 (90.20)	36 (70.59)	

[Frequency (percentage)]

G**roup A** had a significantly higher(86.27%) proportion of patientswith complete abortionas compared to **group B** where only half (54.90%) of the patients had complete abortion. Surgical evacuation was significantly higher in **groupB** (45.10%) as compared to **group A** where merely 13.73% patients required surgical evacuation. **In group A**,78.43% patients had fall in Hb of <1.5gm/dl, while 1.96 % had fall in Hb >4.5 gm/dl, comparison to **group B**, where 60.78% patients had fall in Hb of < 1.5 gm/dl while 3.92% had fall in Hb >4.5 gm/dl. Compared to **group A** (9.80%), a significantly higher proportion (29.41%) of patients in **Group B** required blood transfusion. [Table 4]

DISCUSSION

The aim of the current study was to evaluate the effectiveness of mifepristone plus misoprostol and misoprostol alone for the management of early pregnancy failure. The study involved 102 patients randomized into two groups, with 51 patients in each group. Group A was administered mifepristone plus misoprostol while Group B was given misoprostol alone.

The present study found that the mean age was 28

years inGroup A and 29 years in group B making the groups comparable. Similar findings were observed by JainJK etal.(2002)[12] with mean age of 27 years and 26 years in group A and group B, respectively. Gronlund A et al(2002),[13] Stockheim D et al.(2006)[19] and Schreiber A et al.(2018)[29] found slightly higher age of 30—32 years in their study, while Sinha P et al.(2017)[27]found slightly lower mean age of 25 years in their study.

The present study showed that the maximum patients were multigravida, 86.27% in group A and 78.43% in group B followed by Gravida 2, 9.80% in group A and 15.69% in group B followed by primigravida, 3. 92% in group A and 5.88% in group B, which is not comparable with above study. The study by Hamel C et al. reported that in group A, majority of their patients were Primigravida (43.6%) while only one-fourth(25.6%**)** were multigravida**,** group B also had approximately one-fourth (28.5%) multigravida. This difference might be attributed to the difference in geographical location of the two studies.

The present study showed that in both group A and group B, majority ofpatients were multipara (96.07% vs 94.1%). The parity specificd is tribution of patients in the study by Schreiberetal. showed that more than half of the patients in their study were multipara. Similarly, the study by David Stock holm et al had more than three-quarters of patients as multipara. Multiparity predominated in these studies including the present one assessing the management of early pregnancy failure. There are several factors that can contribute to the risk of spontaneous miscarriages, multiparity is one of them, however, other factors play a much larger role in determining miscarriage risk.

The present study showed mean gestational age of 47 days in group A and 46 days in group B, i.e., more than 6 weeks, which is almost comparable to the following studies. The mean gestational age of patients in the study by Vandenberg et al., Sinha P et al., and Chu J et al. was 6—12 weeks. Spontaneous miscarriage scan occur at any stage during the first trimester, which encompasses the first 12 weeks of pregnancy. The distinction between miscarriages occurring before 6 weeks and those occurring between 6 to 12 weeks can be influenced by different reasons: Miscarriages Before 6 Weeks Spontaneous miscarriages, also known as spontaneous abortions, refer to the loss of a pregnancy before the 20th week of gestation. These can occur at any stage during the first trimester, which encompasses the first 12 weeks of pregnancy. The distinction between miscarriages occurring before 6 weeks and those occurring between 6 to 12 weeks can be influenced by different reasons: miscarriages before 6 Weeks might be due to chromosomal abnormalities, implantation issues, hormonal imbalances, maternal medical conditions, infections, lifestyle factors including smoking, excessive alcohol consumption, and drug use, autoimmune disorders, structural abnormalities in the uterus or cervix; while miscarriages between 6 to 12 Weeksin addition to the above might be due to placental problems, maternal age, etc.

The present study showed that in Group A, 21.57% patients required no repetition, 34.1% patient required single repetition of misoprostol dose, and 45.5% required two doses of repetitions and in group B, 68.63% required no repetition, 19.61% required single repetition of dose, 11.76% required two doses of repetition which is almost comparable to the study mentioned above. Similar findings were reported in the study by P Sinha et al., where, 20.4% requiredno repetition,34.1% required single repletion of dose,45.5 % required two doses of repetition ingroup A, while in group B, 65.9 % no repetition required, 22.7 % required single repetition ofdose,11.4% required two doses of repetitionin group B.

The outcome specific distribution of patients in the studyshowed that in group A, more than half (54.90%)of the patients had complete abortion, one-fourth (25.49%) hadincomplete abortion, and19.61% had persistent gestational sac, whereas ingroup B, comparatively more (86.27%) patients had complete abortion, 7.84% had incomplete abortion, 5.88%had persistent gestational sac which is almost similarto the study by P Sinha et al. where, 57.8% had complete abortion, 24.4% had incomplete abortion ,17.8% hadpersistent gestational sac in group A whereas in group B, 86.7% had complete abortion, 6.7% had in complete abortion, 6.6% had persistent gestational sac.

The present study showed 45.10% had surgical evacuation in group A and 13.73% had surgical evacuation in group B which is almost comparable to the study done by by J.Vandenbergetal. where, 49% in group A and 33.7% in group B required surgical interventions. The study by Hamel C et al. and Chu JJ et al. showed similar results.

The present study showed 9.81% patient had blood loss in group A while 5.88% had blood loss in group B which is almost comparable to the study by Gronlund A etal.[13] where, 7.1% patients in group A and 6.1% in group B had blood loss. However, Vandenberg J et al. in their study reported that 2% patients in group A and14.9%in Group B had blood loss.

The present study showed, 29.41% required blood transfusion in group Awhile 9.8% required blood transfusion in group B. Comparatively, the need for blood transfusion in the study by Hamel C et al. was 0.6 % in group A and 0% in group B, and in the study by Gronlund A et al., blood transfusion was not required by either of the groups.

CONCLUSION

The utilisation of mifepristone pretreatment in cases of early pregnancy failure, in conjunction with misoprostol, has demonstrated an enhanced efficacy in medical management when compared to expectant and surgical management approachesas evident by present and past literature. This is attributed to the

ability of mifepristone to facilitate the action of misoprostol by priming the myometrium, thereby promoting a more effective response.The use of mifepristone pretreatment shown a noteworthy augmentation in the success rate of achieving complete abortion, while concurrently diminishing the necessity for surgical evacuation and its complications such as bleeding, infection, prolonged hospitalization, further doses of misoprostol, and adverse effects.

In the present study a total of 102 patients were enrolled into the present study, to compare the efficacy of mifepristone followed by misoprostol with misoprostol alone for management of early pregnancy failure(≤12 weeks). In the present study, in mifepristone followed by misoprostol group (group A) 86.27% patient had complete abortion where as among patients in misoprostol only group (group B), 54.90% of them had complete abortion. In group A, merely 9.8% patients requiredblood transfusion whereas in group B, 29.41% patients needed blood transfusion. From the findings of the present study and the previous literature, we conclude that the utilization of a combination of mifepristone and misoprostol for the medical management of early pregnancy failure is considered a safe and non-invasive alternative to surgical evacuation and is better than misoprostol alone. Consequently, patients experiencing early pregnancy failure are more likely to acceptor tolerate the treatment.

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