International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Akhter S et al. Int J Reprod Contracept Obstet Gynecol. 2023 Jan;12(1):39-43
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20223472

Original Research Article

Mifepristone alone versus mifepristone-misoprostol combination regimen for management of intrauterine fetal death

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Received: 29 October 2022
Accepted: 29 November 2022

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ABSTRACT

Background: Early pregnancy failure is a common complication of pregnancy. If women do not abort spontaneously, they will undergo medical or surgical treatment in order to remove the products of conception from the uterus. Curettage, although highly effective, is associated with a risk of complications; medical treatment with misoprostol is a safe and less expensive alternative. Unfortunately, after 1 week of expectant management in case of EPF, medical treatment with misoprostol has a complete evacuation rate of approximately 50%. Misoprostol treatment results may be improved by pre-treatment with mifepristone; its effectiveness has already been proven for other indications of pregnancy termination. The study objective was to compare the outcome of Mifepristone alone with the Mifepristone-Misoprostol combination regimen for the management of IUFD.
Methods: This was a Prospective clinical trial at the department of obstetrics and gynecology, Chittagong Medical College Hospital, Chittagong. From March 2016 (Actual patient enrolment started after obtaining ethical clearance i.e. March 2018) to September 2018.
Results: A subjects delivered earlier than group B and the mean induction delivery interval in Group A is significantly less in comparison to Group B (p=<0.001). Out of 50 women, 2(4%) and 10(20%) women in Groups A and B required oxytocin infusion to establish good contractions, and completion of termination who regarded as a failure. In the mifepristone alone group, the success rate is significantly higher than in the combination group.
Conclusions: The efficacy of mifepristone alone was found superior to that of the mifepristone misoprostol combination regimen in the present study.

Keywords: Mifepristone alone, Mifepristone-misoprostol combination, Management, Intrauterine fetal death

INTRODUCTION

Intrauterine fetal death is defined as Ante Partum death of a fetus that occurs beyond 28 weeks of gestation. World health organization (WHO) has defined it as an infant delivered without signs of life after 20 weeks or weighing more than 500 grams when gestation age is not known. Gestational age may vary according to country. For our country and statistical purposes, we consider 28 weeks. Intrauterine fetal death (IUFD) is the most unwanted consequence of pregnancy. The prevalence of IUFD has been reduced and incidence varies in different countries. It is 5 in1000 births in high-income countries and 36 in 1000 births in developing countries.[1,2] After intrauterine fetal death (IUFD), spontaneous expulsion may take

several weeks. During this time retention of the dead fetus could cause emotional distress and intrauterine infection following rupture of the membrane.[3] One of the life-threatening complications that may arise that is, after IUFD, fibrinogen levels may drop leading to coagulopathy.[4] Therefore, medical induction of labour is recommended where there is no contraindication. Induction of labour in IUFD is more difficult than in alive pregnancy. Because most of the IUFD occurs during the late second and early third trimester of pregnancy when the cervix remains unripe and less responsive to oxytocics. Various methods have been tried for the management of intrauterine death. Before the introduction of prostaglandins, IUFD cases were managed by giving repeated high doses of estrogens or more frequently repeated high doses of oxytocin infusion.[5,6] Then prostaglandin has revolutionized and for induction of labour, misoprostol is widely used.[7] Misoprostol has some common side effects- fever, nausea vomiting, dizziness, diarrhoea and headache.[8] The most serious side effect associated with the use of misoprostol is uterine hyper stimulation which can lead to uterine tachysystole and uterine rupture.[9] As a result, there is an increase in interest in mifepristone. Mifepristone is a synthetic steroid with anti-progesterone activity. It competitively blocks both progesterone and glucocorticoid receptors, leading to decidual necrosis, and increases endogenous prostaglandin production and cervical ripening, resulting in the expulsion of the product of conception.[10] In a study conducted by Schreiber et al. (2006) used a mifepristone-misoprostol combination regimen for treatment of early pregnancy failure and found that administration of mifepristone before misoprostol, increases uterine sensitivity to prostaglandin and ripens the cervix early, allowing lower doses of misoprostol for the expulsion of the fetus.[11] McGill et al conducted a study to access the ability of mifepristone to prime the cervix and induce labour in pregnant women and they found that 66% of women entered labour spontaneously and ripened the cervix sufficiently within 48 hours of taking mifepristone.[12] The combination of mifepristone - misoprostol is the common practice in the obstetrics department so far. Some patients develop complications with misoprostol and the induction delivery interval is prolonged. The present study was carried out to emphasize the use of mifepristone alone instead of the combination regimen. The study objective was to compare the outcome of Mifepristone alone with the Mifepristone- Misoprostol combination regimen for the management of IUFD.

METHODS

This is a Prospective clinical trial at the department of obstetrics and gynecology, Chittagong medical college hospital, Chittagong. From March 2016 (Actual patient enrollment started after obtaining ethical clearance i.e. March 2018) to September 2018. Women with a singleton pregnancy with IUFD, gestational age more than 28 weeks and not in labour. The eligible patient was selected from the study population purposively as per inclusion and exclusion criteria. The selected samples were alternatively divided into two groups.

Inclusion and exclusion criteria

Inclusion criteria were gestational age 28 weeks or more with IUFD, singleton pregnancy. Exclusion criteria were women in labour (Bishop's score >6), previous cesarean delivery, multiple pregnancies, history of long-term corticosteroids intake, concurrent anticoagulants, bleeding disorders, chronic liver disease, chronic adrenal failure and inherited porphyrias, IUFD with premature rupture of membrane, having fever or any signs of infection in the body and Contraindication of Mifepristone.

According to the WHO 2015 IUFD defines as an infant delivered without signs of life after 20 weeks or weighing more than 500 grams when gestation age is not known. Gestational age may vary. For our country and statistical purposes, IUFD defines as- Ante Partum death of a fetus beyond 28 weeks is called intrauterine death. Bishop's Score: Bishop score, also known as the cervix score is a pre-labour scoring system to assist in predicting whether induction of labour is required or not. In Bishop's score we see cervical consistency, length, dilatation, position and station of the fetal head. The total score is 0-13. Score: 0-5=unfavorable and 6-13=favorable. Gestational age: Gestational age was calculated from the last menstrual period, or ultrasonography at early weeks. Parity denotes a state of previous pregnancy beyond the age of viability (28 weeks). It is the time interval starting from the first dose of mifepristone up to the delivery of the fetus. After starting the drug development any complications (even nausea, vomiting, fever) up to delivery were considered a side effect. The objectives of the study procedure were explained to all participants in detail. The benefits and possible risks associated with this study were also mentioned. All patients were assured that confidentiality would be maintained strictly. They were also informed that they have the right to withdraw from the study at any time, for any reason. Informed written consent was obtained from each subject. The study protocol was approved by the ethical committee and review committee of Chittagong Medical College.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL) version 23 software for Windows. Socio-demographic and obstetric variables were measured and all data were expressed as mean±SD and percentage ratio. The quantitative values between the two groups were compared by using the Unpaired t-test and the qualitative values were compared by using the Chi-square test (X2). The Odds Ratio was estimated to test the relationship between the experiment and the control group, p value of

<0.05 was considered statistically significant and the confidence interval was set at a 95% level.

RESULTS

The results of the study are arranged in both tables and bar diagrams. Out of 50 women in each group 15 (30%) and 17 (34%) were primi, 14 (28%) and 11 (22%) were para 1, 11 (22%) and 15 (30%) were para 2 and 10 (20%) and 7 (14%) were paras ≥3 in group A and B respectively (Figure 1).

Table 1: Distribution of women according to socio-demographic profile.

Variable	Group A		Group B		P value
Age range (years)	18-34		17-37		
Mean age	23.73±3.81		24.65±4.53		>0.1
Occupation					
Variables	**N**	**%**	**N**	**%**	
Housewife	34	68	37	74	-
Service holder	9	18	6	12	
Business	1	2	3	6	
Others	6	12	4	8	
Education					
Illiterate	12	24	10	20	-
Primary	21	42	19	28	
Secondary	11	22	16	32	
Higher secondary	5	10	4	8	
Graduate	1	2	1	2	
Area of residence					
Urban	37	74	31	62	-
Semi-urban	7	14	10	20	
Rural	6	12	9	18	

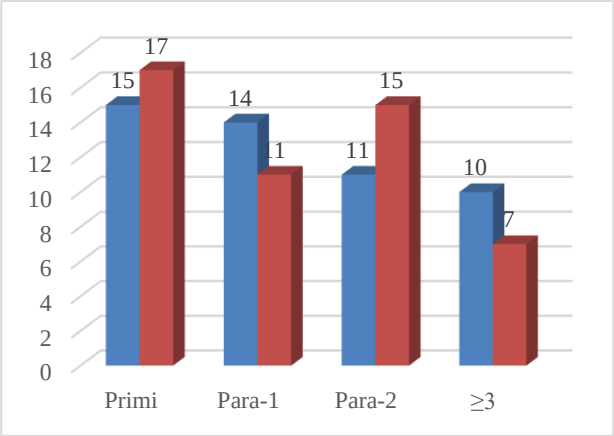

Figure 1: Distribution of gestation and obstetric parameter (distribution of para).

Total 27 (54.66%) and 20 (40%) women presented with <40 weeks; 18 (36%) and 28 (56%) women presented from 40 to 42 weeks and 5 (10%) and 2 (4%) women presented on >42 weeks in Group A and B respectively (Figure 2). Out of 50 women in each group 18 (36%) from Group A and 20 (40%) from Group B had Bishop's score of 2-3 whereas 32 (64%) from Group A and 30 (60%) from Group B had Bishop's score 4-5 at the time of enrollment (Table 2).

Table 2: Distribution of Bishop score in both groups at the time of enrollment.

Bishop's score	Group A		Group B	
	N	**%**	**N**	**%**
2-3	18	36.00	20	40.00
4-5	32	64.00	30	60.00
Mean±SD	3.78±1.97		3.1±1.71	

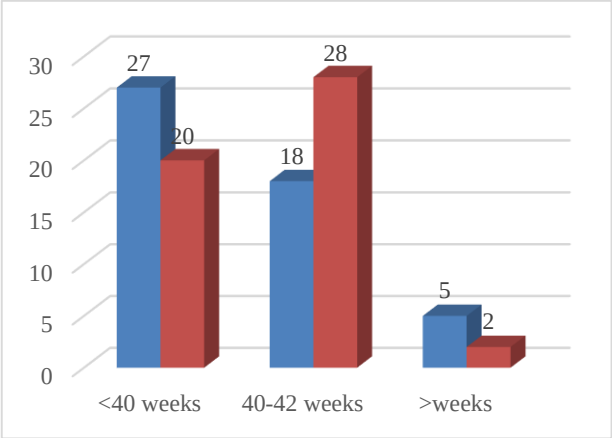

Figure 2: Distribution of gestational age in both groups.

Table 3: Change of Bishop's score after 24 hours of giving mifepristone in Group B.

Bishop's score	Before 24 hours		After 24 hours		P value
	N	**%**	**N**	**%**	
2-3	20	40.00	2	4.00	<0.01
4-5	30	60.00	8	16.00	
6-8	0	0.00	30	60.00	
9-11	0	0.00	10	20.00	
Mean Bishop's score	3.1±1.77		8.67±2.13		

Out of 50 women in Group B 30 (60%) had Bishop's score of 4-5 (Table 3). After 24 hours of applying Mifepritone 30 (60%) women had scores of 6-8 and 10 (20%) had 9-11. Group A subjects delivered earlier than group B and the mean induction delivery interval in Group A is significantly less in comparison to Group B (p=<0.001) (Table 4). Out of 50 women, 2 (4%) and 10 (20%) women in Groups A and B required oxytocin infusion to establish good contractions and completion of termination who regarded as a failure. In the mifepristone alone group, the success rate is significantly higher than in the combination group. Out of 50 women in Group A 2

(4%) and 1 (2%) experienced vomiting and PPH, and in Group B 6(12%) and 2 (4%) women experienced the same respectively (Table 6). But 15 (30%) women in Group B developed fever, whereas none of Group A had this effect. The overall side effects were not significant between the two groups.

Table 4: Mean induction delivery interval (primary outcome).

Induction delivery interval	Group A	Group B	P value
Range (hours)	38-75	56-77	<0.001
Mean induction delivery interval (hours)	47.73±13.21	70.63±14.97	

Table 5: Failure cases that needed augmentation.

Regimen	Successful delivery occurred		Failed (Need oxytocin infusion)		P value
	N	%	N	%	
Mifepristone alone	48	96.00	2	4.00	<0.05
Mifepristone-misoprostol combination	40	80.00	10	20.00	

Table 6: Distribution of different unwanted effects of both regimens.

Unwanted effects	Group-A (Mifepristone) (N=50)		Group-B (Mifepristone plus misoprostol) (N=50)		P value
Vomiting	2	4.00	6	12.00	0.782
Fever	0	0.00	15	30.00	
Retained placenta	0	0.00	2	4.00	
PPH (<1000 ml)	1	2.00	2	4.00	

DISCUSSION

This clinical trial was conducted in the department of obstetrics and gynaecology, CMCH to compare mifepristone alone and mifepristone-misoprostol combination regimens for the management of intrauterine fetal death. In this study, the outcome of the mifepristone alone group was seen and it is evident that the outcome was better than the mifepristone-misoprostol combination regimen. The study findings are discussed and compared with previous published relevant studies in the following section. In this study, 50 subjects were enrolled in each group. Both the groups were comparable in terms of age, occupation, education, parity and gestational age. A shorter induction delivery interval was observed in the mifepristone alone group (Group A) as compared to the mifepristone- misoprostol combination (Group B) group, in our study ($p<0.001$). Similar findings were observed in a recent Indian study by.[13] In the present study, the mean Bishop's score at the time of enrollment was almost similar in both the groups. In the combination group (Group B), after giving mifepristone Bishop's score changed significantly. This indicates that mifepristone has a cervical dilatation effect. Some related studies conducted by Nagaria et al and Mandade et al found similar results.[14,15] In the mifepristone alone group, the patient started labour earlier than in the combination group. As a result, the mean induction delivery interval was found shorter which was 47.73±13.21 hours than the combination group which was 70.63±14.97 hours. This result is statistically significant. A similar study was also conducted recently by Ahuja et al.[13] They conducted the study with 60 cases and reported that mifepristone has a significantly shorter induction delivery interval than the combination group. In the present study, 4% of women from Group A and 20% from Group B failed to deliver within 48 hours of completion of the dose. They required oxytocin infusion for augmentation and completion of delivery. The success rate is significantly higher in the mifepristone alone group. Subrat et al in their study found only 3 cases required oxytocin in the misoprostol alone group and no oxytocin was required in the mifepristone combination group.[16] Side effects in our study were observed less in the mifepristone alone group than in the combination group. But overall side effects were not significant between the two groups. No cases of retained placenta were found in the mifepristone alone group which is similar to the previous related studies conducted by Sharma et al and Carbol et al.[3,17] Only 2% of subjects of the mifepristone alone group developed post-partum haemorrhage (PPH) and 4% of the combination group developed the same complication. A related study by Mandade et al reported that with mifepristone, the incidence of PPH is less.[18] This means that our results are supported by previous results. Though the exact mode of action of mifepristone in the induction of labour in intrauterine death is unclear, according to various studies, mifepristone causes blockage of progesterone receptors directly leading to endometrial decidual degeneration, cervical softening and dilatation with the release of endogenous prostaglandins. This may be responsible for the complete shedding of the placenta and membranes.

Limitations

Limitations of current study were small sample size, which was not powered enough to evaluate the adverse events and women with a scarred uterus were not included in this study.

CONCLUSION

In conclusion, the efficacy of mifepristone alone was found superior to that of the mifepristone- misoprostol combination regimen in the present study. The mean induction delivery interval was significantly less in mifepristone alone in comparison to the combination group. Side effects were observed less in the mifepristone alone group but as a whole, this is not significant in comparison to the combination group. With mifepristone alone, side effects were not significant as in the combination group. So another study with a large sample size and randomized controlled trial may be done.

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

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Cite this article as: Akhter S, Islam M, Zaman L, Alam SKT, Banu FA. Mifepristone alone versus mifepristone-misoprostol combination regimen for management of intrauterine fetal death. Int J Reprod Contracept Obstet Gynecol 2023;12:39-43.