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Role of combination of mifepristone and misoprostol versus misoprostol alone in induction of labor in late intrauterine fetal death: A randomized trial

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Abstract
Objectives: To compare the efficacy, safety of a combination of mifepristone and misoprostol with oral misoprostol alone for induction of labor in late IUFD cases.
Methods: A hospital based prospective randomized comparative study over 120 pregnant women with IUFD after 28 weeks of gestation requiring induction of labor for termination of pregnancy. Women were divided into two groups. Women of group1 (n=63) received a single oral dose of 200 mg of mifepristone, and after 24 hours, 50 mcg of intravaginal misoprostol was administered followed by 50 mcg of intravaginal misoprostol at 6 hours interval for a maximum of 5 doses if required. For group 2 (misoprostol alone group, n=57) received only misoprostol in the dose of 50 mcg intravaginally every 6 hours for a maximum of 5 doses (5x50 mcg=250 mcg in 24hours).Primary outcome was measured by the rate of successful delivery in 24 hours and induction delivery interval from first dose of misoprostol to complete delivery of fetus and placenta.
Results: Successful delivery occurred within 24 hours, who received mifepristone before misoprostol than misoprostol alone (94% versus 81%; difference12.95%; 95% CI, 1.07%-24.83%). Mean induction delivery interval in combined regime (group 1) and misoprostol only regime(group 2) was 12.45h (95% CI of mean, 10.863h-14.038h) and 20.25h (95% CI of mean,18.284h-22.216h) respectively; P=0.0001. Mean dose of misoprostol required in group 1 was 2.41± 1.19 and 3.67± 1.07 in group 2 (P=0.0001).With respect to side effects, the two groups did not differ significantly.
Conclusions: Addition of mifepristone to misoprostol appears to be more effective than misoprostol alone for induction of labor in late IUFD cases but both the regimens were equally safe, easy to administer and affordable.

Keywords: mifepristone, misoprostol, intrauterine fetal death, induction of labor

Introduction
Intrauterine fetal death is one of the most devastating obstetric complications. A clinically accepted definition of IUFD is the death of fetus at or after 20 weeks of pregnancy [1], but for international comparison WHO has now recommended IUFD as a baby born with no sign of life at or after 28 weeks of gestation [2]. The loss of a wanted baby at any gestational age is distressing not only to the expectant parents, but also to their relatives and attending obstetrician. Despite improvement of medical facilities, pregnancy wastage still occurs at an unacceptably high rate. Common causes of IUFD include maternal systemic illness such as diabetes mellitus and hypertension and fetal causes such as infection, immune haemolytic disease, cord accidents, metabolic disorders, malformation and placental dysfunction [3].
As over 90% of women with IUFD deliver spontaneously within 3 weeks of the event. Until then the retention of dead fetus could cause emotional distress and intrauterine infection following rupture of membrane [4]. About one in four women with a dead fetus retained for 4 weeks or more may develop consumptive coagulopathy [3]. To reduce these complications medical induction is recommended, if it is considered safe [4]. The ideal drug for termination of pregnancy should not only be effective and safe but should be affordable to avoid financial burden to the patients. Induction by oxytocin was widely used in the past, but it was less successful as the uterus is less sensitive to oxytocin before term. RCOG in its green top guide line No.55 endorsed a combination of mifepristone and a prostaglandin preparation as the first line of intervention for induction of labor in IUFD, which is also recommended by NICE guidelines especially for late IUFD cases [5, 6]. WHO recommends oral or vaginal misoprostol for induction of labor in the third trimester of pregnancy in women with dead or malformed fetus [7].

Due to the varying schools of thoughts regarding drug treatment, the present study is undertaken to evaluate and compare efficacies of both the regimen (combined mifepristone and misoprostol and misoprostol regimes only) in an effort to find a better management of woman with IUFD along with the advantages and disadvantages of one method over the other.

Materials and Methods

The study was conducted primarily on 123 pregnant women diagnosed with intrauterine fetal death who were admitted in the labor ward in the Department of Obstetrics and Gynecology at Burdwan Medical College, Burdwan and R.G.Kar Medical College, Kolkata through OPD and emergency after 28 weeks of gestation over a period of one and half years (from January 2017 to June 20180). Three mothers were excluded from the study due to refusal of enrolment. Finally a total of 120 pregnant women were randomly allocated into two groups [Group 1, combination group of mifepristone and misoprostol, n=63 women) and group 2 (mifepristone only, n=57 women)]. The study was designed as a prospective, interventional randomized comparative study. The randomization was done by computer generated random numbers. After proper counselling and informed consent from pregnant mothers selected in the study population, detailed history-taking, physical and obstetrical examinations were performed and all routine base line investigations were included according to our hospital protocol in IUFD cases. Inclusion criteria included in the study were women with intrauterine fetal death confirmed by ultrasound examination, period of gestation of 28 weeks or more determined by first day of last normal menstrual period, clinical examination and USG and women who were not in labor. Grand multipara (parity >4), H/O allergy to prostaglandins, congenital uterine anomaly, women with medical disorders like severe anemia, cardiovascular problem, bronchial asthma, glaucoma and disorders in pregnancy like previous uterine scar, multiple pregnancies, placenta previa, transverse lie, evidence of coagulopathy and period of gestation below 28 weeks were excluded from our study.

For the termination of pregnancy group 1 received both mifepristone and misoprostol. Mifepristone (200mg) single dose was used orally and after an interval of 24 hours misoprostol (50 mcg) was inserted intravaginally in the posterior fornix every 6 hours for a maximum of 5 doses per course. For group 2(misoprostol alone group) received only misoprostol in the dose of 50 mcg intravaginally every 6 hours for a maximum of 5 doses/ course. Before administration of subsequent doses of misoprostol, vitals of mother were checked. Vaginal bleeding, appearance of side effects like nausea, vomiting, headache diarrhea, shivering and fever were recorded. The study was approved by ethics committee of the institution.

Successful induction was defined as complete delivery of fetus and placenta within 24 hours of commencement of first dose of misoprostol. If the fetus was undelivered in 24 hours of first dose of misoprostol, it was treated as failure. For the purpose of delivery of failure cases, second course of misoprostol was started after a gap of 12 hours from the last dose of misoprostol in the first course. Other methods of intervention were considered if successive two courses of misoprostol failed to deliver the fetus and placenta.

Primary outcome was measured by the rate of successful delivery in 24 hours and induction delivery interval (from first dose of misoprostol to complete delivery of fetus and placenta).

Secondary outcome was measured by the total dose of misoprostol required, rate of requirement of additional intervention, adverse effects related to drugs and complications (immediate and late upto 6 weeks).

Statistical analysis

For sample size calculation, patient required in order to having 80% power of detecting clinically important difference in success rate of 25% between two groups at 5% level of significance, assuming a success rate of 40% in the group having the least successful treatment, a total of 123 pregnant women were included in the study, Sample size calculation was done by electronic calculator of software Stat Calc (7.1.1 version). Continuous variables are expressed as mean, median and standard deviation and compared across the group by Student's t- test. Chi -square analysis was also done to assess the significance of variables. Relative risk and odds ratio with 95% CI were calculated for outcome of parameters. Software (MedCalc and Stat Calc version 7.1.1) was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Both groups were comparable with respect to socio demographic characteristics and obstetrical parameters and the comparison is shown in Table 1.

The outcome was shown in Table 2. Successful delivery within 24 hours of commencement of the first dose of misoprostol without additional intervention occurred in 93.65 % (59/63) of women who received mifepristone prior to misoprostol and 80.71% (46/57) of women who received misoprostol only; the difference is statistically significant (p=0.0450). The mean induction delivery interval (IDI) was significantly shorter with the use of combined regime than the use of misoprostol only regime (12.45± 6.25 h and 20.25± 7.28 h respectively; P= 0.0001). The mean number of misoprostol doses required for delivery was significantly less in women who received mifepristone compared with those who received misoprostol only (2.41± 1.19 vs. 3.67± 1.07, P= 0.0001). In combination group 38.1 % of women were delivered by 2 doses (100mcg) whereas it was 10.53% in misoprostol alone group. Maximum delivery (38.6%) occurred in misoprostol alone group by three doses. In misoprostol alone group, 31.58% of women were delivered after 4 doses of misoprostol as compared to 11% of women in combination group (P=0.001).

Both the groups are comparable in respect to adverse effects. In misoprostol alone group 5(8.77%) women suffered from shivering whereas it was noted only in 3.17% in women of combination group who received mifepristone prior to misoprostol. However the difference was not statistically significant (P=0.193) [Table 3].

Table 4 and Fig1 compare the primary outcome of vaginal delivery in different studies of combined and misoprostol only regimes. However, the incidence of total events was not significantly different between combination and misoprostol alone groups (87.23% versus 84.21%; odds ratio 1.2813; 95% CI, 0.6493 to 2.5281; P=0.4748, z stat, 0.715), 3RCTS, 274 pregnant women). The Y –axis of the '*forest plot'* corresponds to the treatment effect where the blue dotted line down to the middle of the picture is known as the *'line of no effect*' and in this case is associated with odds ratio of 1.0. The horizontal lines show 95% confidence interval of the estimate with the *blob* in each line (—■—) is the *point estimate* of the difference of the groups. The *point estimate* varies from 0.5-4 in different studies including the present study but 95% confidence interval of our study covers a wide range (1.0543 to 11.7998).

Discussion

Different methods were conducted in the past for induction of labor in late IUFD cases. In the present study the mean induction delivery interval(IDI) was significantly shorter with the use of combined regime than with the misoprostol only regime (12.45h vs.20.25 h, P=0.0001).Delivery within 12 hours of misoprostol administration occurred significantly in higher proportion of women receiving the mifepristone pre-treatment on comparison to misoprostol alone (55.56% vs.10.53%, p=0.001).Comparable results were reported by various studies (Agarwal A *et al.*, Sharma D *et al.*, Parveena G *et al.* and Panda S *et al.*) but the mean interval varies in all these studies [8-11]. The probable reason in difference is mainly due to the difference in doses, schedule of misoprostol administration and adjustment of misoprostol dose according to gestational age by various study guidelines [5-7]. The number of misoprostol doses required in both the groups was compared and was found to be significantly least dose was required in women with mifepristone in the present study. Similar result was also observed by Vayrynen *et a1* [12] in the year 2007. Mifepristone administered before misoprostol increases the sensitivity of the uterus to prostaglandins and ripens the cervix allowing lower doses of misoprostol to induce expulsion of fetus. In the present study mean dose given in combination group and misoprostol alone group were 2.41± 1.19 and 3.67±1.07 respectively. Our results correspond with the findings of Gupta *et al.* [13] and Agarwal *et al.* [8]. Mean induction delivery interval in combination and misoprostol group alone was higher in our study (12.45 h vs. 20.63h) whereas it was lower by the study of Gandhi *et al.* [14] (10.55h vs.12.55h) and Gupta *et al.* [13] (9.6h vs. 16.2 h). This difference in the present study is mainly due to administration of lower dose of misoprostol (50 mcg) for induction of labor. The interval between administration of mifepristone and misoprostol was only 24 hours in our trial which also differs from majority of the studies [9, 15]. The rate of successful delivery with the combined regime in the present study was 93.65% which was comparable with the findings of Gupta S *et al.* [13], but differs from Agarwal A *et al.* [8] who noted 85.7% delivered within 24 hours of first dose of misoprostol in combined group.

Our regimen carried mild gastro intestinal symptoms nausea in combination group, but shivering and pyrexia were more frequent in misoprostol group only. As the side effects of misoprostol are dose related, a marginally higher incidence of such side effects were observed in misoprostol group only in the present study as well as in a few other studies [9, 14, 15]. The complication like uterine rupture was not noted in our study and no case in the study group suffered from PPH or coagulopathy.

Figure 1, shows the confidence interval of the different results (the horizontal lines). Some of the lines cross the line of no effect (i.e. the vertical line), which mean either there is no significant difference between the treatments and/or that the sample size was too small to allow us to be confident where the true result lies. Only the present trials showed a statistically significant benefit (in terms of vaginal delivery) (Table 4). The *diamond* below the horizontal lines represents the *pooled data* of all the three trials (overall odds ratio in combined regime: misoprostol alone=1.2813), with a new much narrower confidence interval of odds ratio (0.6493- 2.5281). Since the *diamond* (◆) firmly overlaps the line of *no effect*, we can say that there is probably a little to choose between the two treatment regimes in terms of primary end point of successful delivery in 24 hours.

Delivery of IUFD babies is a frustrating job as uterus is not sensitive by usual methods of induction of labor before term. Different suggested induction of labor regimens have been recommended for delivery of IUFD cases, but still there is no consensus regarding the ideal regimen [17].

Table 1: Socio-demographic and obstetric parameters of participants

Variables	Group 1 (Mifepristone + misoprostol, n=63)	Group 2 (Misoprostol only, n=57)	P-value
Age (Years)	20.86± 2.53	20.84±2.51	0.965
Parity	1.33±0.596	1.28± 0.491	0.615
Primipara	46(73.02)	42(73.68)	0.934
Gestational age(weeks)	32.95± 2.64	33.14±2.61	0.692
<32 weeks	31(49.21)	25(43.86)	0.557
>33 weeks	32(50.79)	32(56.14)	
BMI)Kg/m^2)	21.14±1.72	21.55±1.95	0.226
Birth weight (Kg)	1.78±0.45	1.75± 0.44	0.712
Hemoglobin(gm/dl)	11.009±0.982	11.039±0.995	0.869

N (%)

Table 2: Outcome measures

Variables	Group 1 (Mifepristone + misoprostol, n=63)	Group 2 (Misoprostol, n=57)	RR(95%CI)	P-value	Z-stat	Risk difference (95% CI) (%)
Incidence of successful delivery in 24 hours	**59(93.65)**	**46(80.71)**	**0.3290(0.110-0.976)**	**0.0450**	**2.005**	**12.95 (1.07 to 24.83)**
Mean Induction-delivery	Mean ± SD	Mean ± SD		P-value		
interval(h)	12.45± 6.25	20.25± 7.28		0.0001		
<12	35(55.56)	6(10.53)		0.001		
12-24	24(38.09)	40(70.18)				
24-36	4(6.35)[a]	8(14.04)[a]				
36-48	0	3(5.26)[b]				
[a] 4 pregnant women in combination group and 8 women in misoprostol alone group did not require any additional course of misoprostol and delivered within 24-36 hours; [b] 3(5.26%) in misoprostol group only required 2nd course of misoprostol and delivered within 36 -48 hours						
Mean number of	Mean ± SD	Mean ± SD		P value		
doses of Misoprostol	2.41± 1.19	3.67± 1.07		0.0001		
0	2 (3.17)[c]	0		0.001		
1	11(17.46)	0				

2	24(38.1)	6(10.53)				
3	15(23.81)	22(38.6)				
4	7(11.11)	18(31.58)				
≥5	4(6.35)[d]	11(19.3)				

n (%); CI, confidence interval; [c] 2 pregnant mother in combination group delivered with mifepristone only; [d] 4 women in combination group required 5 doses of misoprostol instead of 4 doses.

Table 3: Incidence of adverse effects of misoprostol administration

Variables	Group 1 (n=63) (Mifepristone+ misoprostol)	Group 2 (n=57) (Misoprostol only)	RR(95% CI)	P-value
Nausea	2(3.17)	2(3.51)	0.95(0.35-2.57)	0.919
Pyrexia	1(1.59)	2(3.51)	0.63(0.13-3.15)	0.502
Shivering	2(3.17)	5(8.77)	0.53(0.16-1.73)	0.193
Nil	58(92.07)	48(84.21)	1.53(0.74-3.16)	0.182

RR, relative risks; CI, confidence interval

Table 4: Comparison of 3 RCTs regarding mode of delivery between two groups

Study or subgroup	Combination groups		Misoprostol group		Odds ratio M-H, Random, 95% CI	P-value	Z -value
	Events	Total	Events	Total			
Arjunan Y *et al.* (2018) [16]	28	36	31	36	0.5645 [0.1652, 1.9286]	0.3617	0.912
Agarwal A *et al.* (2014) [8]	36	42	35	40	0.8571 [0.2396, 3.066]	0.8126	0.237
Present study Modak R *et al.* (2018)	59	63	46	57	3.5272 [1.0543, 11.7998]	0.0408	2.046
Total(95% CI)		141		133	1.2813[0.6493, 2.5281]	0.4748	0.715
Total events	123		112				

Chi -square= 1.264, DF= 2, P=0.532

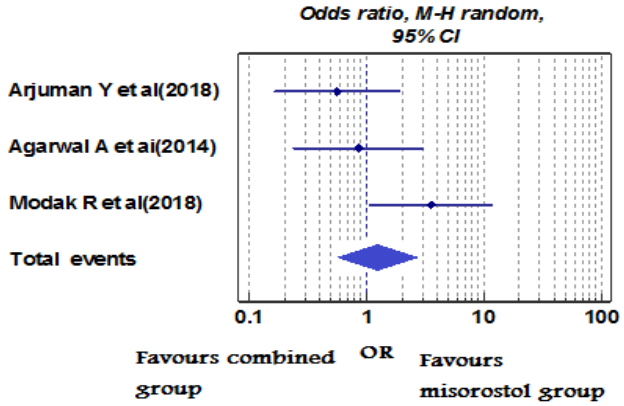

Fig 1: The forest plot of the odds ratio of 3 randomized controlled trials in which each compared with combination group against misoprostol group alone in the treatment of IUFD fetuses.

M-H. Mantel Haenszel; OR, odds ratio; CI, confidence interval

Conclusion

Both the regimens were equally safe, less invasive, effective, practical and inexpensive, but the combination regime is more effective in terms of tolerance and efficacy with regard to early onset of labor and shorter induction delivery interval. However the combined regimen requires less dose of misoprostol than misoprostol regime alone for induction of labor without any increase in adverse effect. Further large-scale, multicenter randomized studies are needed for better treatment option, optimum dosage and dosing interval of the two drugs for a better management of IUFD cases.

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Ethical approval: The study was approved by Institutional Ethics Committee

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