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Original Article

Comparison of mifepristone combination with misoprostol and misoprostol alone in the management of intrauterine death
Condensation – misoprostol and mifepristone combination is more effective than misoprostol alone in the management of intrauterine death

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Abstract

Objectives: To compare the efficacy and safety of misoprostol and mifepristone combination with misoprostol alone in management of intrauterine death.

Materials and Methods: It is a prospective study carried out in 40 pregnant women admitted with intrauterine death after 28 weeks of gestation at a tertiary care referral centre divided into two groups of 20 each. Every alternate patient was assigned Group I and Group II. Group I (combination group) – the women received 200 mg of mifepristone; and after 36 hours, misoprostol was administered orally (100 μg if pregnancy was <37 weeks and 50 μg if pregnancy was >37 weeks) for every 3 hour till they went into active labor for a maximum of four doses. Group II (misoprostol group) – Women received oral misoprostol (100 μg if pregnancy was <37 weeks and 50 μg if pregnancy was >37 weeks) for every three hours till she went into active labor for maximum of four doses.

Primary outcome measures were achievement of successful induction and induction delivery interval (IDI). Women who did not deliver after four doses of misoprostol were considered as failure. In all the women, bishop score before the start of mifepristone and misoprostol, induction delivery interval, and adverse effect of the drug were noted. Data were analyzed by using Student *t* test and Chi-square test.

Results: In the Group I, 60% of women, delivered with mifepristone alone. The rest of the patients [8 (40%)] had significant improvement of the bishop score after 36 hour. Parity, gestation, and bishop score did not affect the success of induction in the Group I. IDI was significantly less in the Group I (6.72 ± 3.34) as compared with that of the Group II (11.81 ± 6.33). Parity, gestation, and bishop score did not affect the IDI in the two groups. Number of doses of misoprostol required were significantly less in patients who were pretreated with mifepristone.

Conclusion: Combination of mifepristone and misoprostol is more effective than the misoprostol alone for induction of labor in women with intrauterine death.

Keywords: Intrauterine death; Mifepristone; Misoprostol

Introduction

The antepartum death occurring beyond 28 weeks is termed as intrauterine death for all practical purposes. A number of maternal, placental, and fetal conditions can result in fetal demise, but in about 25–35% of cases, the cause remains unknown [1].

Intrauterine death can lead to various complications like psychological upset and intrauterine infections. If dead fetus is retained in uterus for more than 4 weeks, it can lead to consumptive coagulopathy and disseminated intravascular coagulation [2]. When the fetal death occurs, spontaneous expulsion will usually occur in most cases i.e. in about 80% of

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cases, within 2 weeks of death. But, it can be evacuated earlier at the request of women to relieve emotional distress.

Various methods have been tried in the management of intrauterine death. Before the introduction of the prostaglandins, women with intrauterine death were managed by giving repeated high doses of estrogens [3], intra amniotic injection of hypertonic solutions [4], use of hygroscopic tents [5], bougies, catheter, and balloon [6,7], or more frequently with repeated high dose infusion of oxytocin [8,9].

Now the prostaglandins have revolutionized the management of intrauterine death. They can be used by oral, sublingual, intravenous, intramuscular, vaginal, and rectal routes. Nausea and vomiting is the main side effect of prostaglandins. The role of antiprogestin, mifepristone for uterine priming was first reported by Cabrol et al [10], who reported successful induction of labor using mifepristone 200 mg 12-hourly for 2 days. Subsequently it was observed that combination of mifepristone and misoprostol for induction of labor in late intrauterine death is more effective and safe regimen and the induction to delivery interval is shorter than the studies using mifepristone or misoprostol alone [11]. Mifepristone, an antiprogestrone steroid, increases uterine activity, sansitizes the myometrium to prostaglandins action, and induces cervical ripening with minimal side effects. It is of great interest in reducing duration of termination and increasing comfort for the patient. Keeping this fact in mind the present study was planned.

Material and methods

The present prospective study was carried out in 40 pregnant women admitted with intrauterine death after 28 weeks of gestation in labor ward of department of Obstetrics & Gynecology at a Tertiary Care Referral Center after ethical clearance. The women were divided randomly, alternatively, into two groups of 20 each, the patient came first was assigned Group I, the next patient Group II, then Group I, and so on. Total number of patients was decided by power analysis.

Group I (combination group) – it included 20 women, who were induced with mifepristone and misoprostol combination. The women received 200 mg of mifepristone; and after 36 hours, misoprostol was administered orally (100 μg if pregnancy was <37 weeks and 50 μg if pregnancy was>37 weeks) for every 3 hours, till they went into active labor for a maximum of four doses.

Group II (Misoprostol group) – It included 20 women who received oral misoprostol (100 μg if pregnancy was<37 weeks and 50 μg if pregnancy was>37 weeks) 3 hourly, till she went into active labor for a maximum of four doses. Every alternate patient was assigned the respective group.

Women with previously scarred uterus, multiple gestation, glaucoma, asthma, epilepsy, heart disease, and grand multipara were excluded from the study.

Primary outcome measures were achievement of successful induction and induction delivery interval. Success of induction was defined as vaginal delivery occurring within 36 hours of administration of mifepristone and within 24 hours of administration of first dose of misoprostol.

Table 1
Distribution of various parameters in two groups

Parameter	Group I	Group II	p, t
Age (y)	22.85 ± 2.79	23.6 ± 3.25	0.05, |0.782|
Parity	0.65 ± 0.81	0.55 ± 0.94	0.05, |0.359|
Gestation	33.35 ± 3.63	34.60 ± 3.94	0.05, |1.043|
BMI	20 ± 1.17	19.95 ± 1.10	0.05, |0.139|
Initial bishop score	1.45 ± 1.60	2.1 ± 1.20	0.05, |0.25|
Induction delivery interval	6.72 ± 3.34 (8 patients)	11.81 ± 6.33	0.05, |2.73|
No. of doses of misoprostol	1.6 ± 0.92	3 ± 0.95	0.01, |3.32|

Data were represented as mean ± standard deviation.
BMI = body mass index.

Women who did not deliver after four doses of misoprostol were considered as failure of regimen. In all the women details of the demographic profile, bishop score before the start of mifepristone and misoprostol, induction delivery interval, and adverse effect of the drug were noted. The induction delivery interval and success of induction was also correlated with bishop score [<3 (very poor bishop) and 0.3] at the start of the treatment in the two groups. Data were analyzed by using Student t test and Chi-square test.

Results

Results are shown in Tables 1–3. Both the groups were comparable in terms of age, parity, gestation age, and bishop score (Table 1). There were 45% primigravida and 55% multigravida in the Group I and 70% primigravida and 30% multigravida in the Group II. Most patients (80%) had bishop score 0–3 in the two groups. In the Group I 60% of (12) women, delivered with mifepristone only, thus had 60% success of induction. Success of induction with mifepristone was not related to age, parity, and bishop score (Table 2, $p > 0.05$). In the Group I, there were four patients who had bishop score>3 and all of these patients delivered with mifepristone, whereas 16 patients had bishop score 0–3 of which only 8 patients (50%) delivered after giving mifepristone. The rest of the 8 patients, who did not deliver with mifepristone, had bishop score 0 before the start of treatment and 2.63 ± 2.26 after 36 hours of treatment. The change is highly significant ($p < 0.01$). On correlating the success of induction in the Group I (12 patients), with parity, gestation,

Table 2
Correlation of successful induction after mifepristone with bishop score, parity, and gestation age

Parameter (n)		Successful (12 women)	Unsuccessful (8 women)	p
Parity	Primi (9)	5	4	$p > 0.05$, χ^2–0.134
	Multi (11)	7	4	
Gestation	<34 wk (10)	4	6	$p > 0.05$, χ^2–1.080
	>34 wk (10)	8	2	
Bishop score	<3 (16)	8	8	$p > 0.05$, χ^2–3.33
	>3 (4)	4	0	

Table 3
Correlation of IDI (h) in the two groups with parity, gestation, and bishop score

Parameter (*n*)		Group I IDI (h)	Group II IDI (h)	*p*, *t*
Bishop score	<3	8.07 ± 3.47 (4)	13.41 ± 6.29 (14)	0.128 (>0.05), |1.605|
	>3	4.92 ± 2.81 (4)	8.06 ± 5.07 (6)	
Gestation	<34 wk	7.60 ± 2.98 (6)	11.69 ± 6.49 (10)	0.172 (>0.05), |1.438|
	>34 wk	3.2 ± 2.54 (2)	11.93 ± 6.51 (10)	
Parity	Primi	8.65 ± 3.19 (4)	12.71 ± 6.03 (14)	0.220 (>0.05), |1.276|
	Multi	4.35 ± 2.02 (4)	9.72 ± 7.09 (6)	

IDI = induction delivery interval.

and bishop score, there was no significant difference (Table 2). For induction delivery interval (IDI) evaluation, eight women were left in the Group I, IDI was significantly less in the Group I as compared with that of the Group II ($p < 0.05$) (Table 1). On comparing the IDI in the two groups in term of parity, gestation, and bishop score, there was no significant difference (Table 3).

All the women in the study had success of induction i.e. delivered within 24 hours after first dose of misoprostol. As far as the side effects are concerned, only two women experienced vomiting and diarrhea, one each with mifepristone (Group I). With misoprostol, the side effects like nausea, vomiting, headache, diarrhea, and fever were experienced by 10.75%, 25%, 14.29%, 7.15%, and 17.86% of women, respectively.

Discussion

The study was carried out to find the IDI in patients with intrauterine death who were treated with misoprostol alone or combination of mifepristone and misoprostol. The primary outcome measure was the achievement of successful induction and induction delivery interval. The success of induction was defined as vaginal delivery occurring within 36 hours of administration of mifepristone or within 24 hours of administration of first dose of misoprostol.

Mifepristone is an antiprogestational steroid, which induces cervical ripening and increases uterine activity, thus leading to the expulsion of fetus [12,13]. In the Group I 12/20 (60%) patients achieved successful induction with mifepristone alone, within 36 hours. Similar results were also shown by other authors [14,15]. In 1989, Padayachi et al [14] studied mifepristone in a dosage of 400 mg/d to induce labor in patients with intrauterine death in late pregnancy and found that 8 of 12 patients (66.7%) delivered within 72 hours of treatment, whereas only 2 of 12 patients (16.7%) delivered, who were treated with placebo .In 1990, Cabrol et al [15] studied 94 women with intrauterine death and found that mifepristone given 200 mg 3× a day for 2 days resulted in 29 of 46 (63%) patients delivering within 72 hours of start of treatment compared with only 17% patients delivering within 72 hours, who were treated with placebo.

In present study, the mean induction delivery interval was 6.72 [3.34 (1.4−13)] and 11.81 [6.33 (4−25.30)] hours in the Group I and Group II, respectively (Table 1) and the difference was highly significant. The result of our study is not comparable to the study of Vayrynen et al, who studied 130 women with intrauterine fetal death (21−42 weeks of gestation) 16. In their study, 82 women received 100 g misoprostol at 4-hour interval and 48 women received 200 mg mifepristone followed 19 hours later by misoprostol 25 g at 4-hour interval and found that induction to delivery interval did not differ between the two groups (13.3 hours *vs.* 12.8 hours). The reason for the similar induction delivery interval in both groups may be the lower dose of misoprostol as they have used only 25 g misoprostol in group which was pretreated with mifepristone, whereas 100 g misoprostol in another group which was not pretreated with mifepristone.

In 2002, Wagaarachchi et al [11] studied the combination of mifepristone and misoprostol in 96 patients with intrauterine death and found that IDI was shorter with increasing gestation ($p = 0.001$). In the present study, induction delivery interval was not affected by the gestation, parity and bishop (Table 2). The mean number of doses of misoprostol required in the Group I and Group II was 1.6(0.92) and 3(0.95), respectively ($p < 0.01$, highly significant, Table 1), in present study. The similar results were also noted by Vayrynen et al, in 2007, who found that doses of misoprostol needed were less in the group which was pretreated with mifepristone ($p = 0.0028$) [16].

So, both mifepristone in combination with misoprostol and misoprostol alone achieved successful induction in women with intrauterine fetal death. Mifepristone alone led to delivery of baby in 60% of patients in the Group I. Mifepristone led to significant improvement in bishop score in patients who were not delivered by this drug. The combination therapy led to short induction delivery interval than that of misoprostol alone. In addition, the number of doses of misoprostol required was less in patients who were pretreated with mifepristone.

To conclude, combination therapy of mifepristone and misoprostol is more effective than the misoprostol alone for induction of labor in women with intrauterine fetal death.

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