Role of Combination OF Mifepristone and Misoprostol Verses Misoprostol alone in Induction of Labour in Late Intrauterin Fetal Death: A Prospective Study

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Abstract

Objective: To compare efficacy, safety and tolerance of combination of mifepristone and misoprostol versus misoprostol-only in induction of late intrauterine fetal death (IUFD).

Materials and methods: This prospective study included a consecutive series of 52 women gravid up to fourth with IUFD after 28 weeks of gestation between January 2008 and June 2011. Women were divided into two groups. First group of women received a single oral dose of 200mg mifepristone, and after 24 hours, 100ug of intravaginal misoprostol was administered, followed by intravaginal 100µg misoprostol at four hourly intervals if required. Second group of women received 100 µg misoprostol at four hourly interval per vaginally (maximum 600µg in 24 hours). Oxytocin was given for augmentation if needed.

Results: The induction-to-delivery time was shorter with the combination regimen ($p < 0.001$) group. The total dose of misoprostol needed was lower in the group pre-treated with mifepristone ($p < 0.001$). Oxytocin was required only in misoprostol group. The two groups did not differ as regards complications experienced during labor and delivery significantly.

Conclusion: Both regimens, misoprostol-only and the combination of mifepristone and misoprostol are safe in induction of labor after intrauterine fetal death (IUFD). Pre-treatment with mifepristone is more effective in terms of reducing of induction delivery interval, requirement of lesser dose of misoprostol and no need of augmentation with oxytocin.

Keywords: Intrauterine Fetal Death, Mifepristone, Misprostol, Induction of Labour

Introduction

"Tear in eyes but milk in blessing". This describes greatness of motherhood. To achieve motherhood women are ready to go through labor pain which is described often as more severe than the pain of angina.

Scenario is different in intrauterine death cases. As in IUFD journey of labor pain will be fruitless. So, it is of utmost important to search for the method which can reduce hour of pain in labor of IUFD cases, Oral misoprostol administration for labor induction with an IUFD was first described in Sao Paulo, Brazil in 1987. Since that time, misoprostol use for obstetrical purposes has grown widely. Repeated dose requirement and side effects such as uterine over activity (hyper stimulation, hyper tonus and tachysystole) and systemic response (nausea, vomiting, diarrhea and shivering) always remains

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issue of concerns. Mifepristone is a steroid compound, which competes with progesterone at the receptor level and is widely used for first and second trimester termination of pregnancy (1, 2). Mifepristone, administered before misoprostol, increases the sensitivity of the uterus to prostaglandins and ripens the cervix, thereby allowing lower doses of misoprostol to induce expulsion of the fetus. Aim of my study is to evaluate safety, tolerance and efficacy of combination regimen of mifepristone and misoprostol with conventional use of misoprostol alone.

Materials and methods

This prospective study included a consecutive series of 52 women with IUFD after 28 weeks of gestation attending to Department of Obstetrics and Gynecology, Neigrihms, India, between January 2008 and June 2011.

Inclusion criteria were as follows: (i) gravid up to fourth, (ii) without previous lower segment cesarean section (LSCS), (iii) not in labor (no regular contractions or unfavorable cervix) and (vi) willing for medical management..

Exclusion criteria were assigned as abnormal coagulation profile and allergy to prostaglandin.

Period of gestation was assessed by last menstrual period. The diagnosis of intrauterine fetal death (IUFD) was confirmed through an ultrasound by the absence of a fetal heart pulsation. After giving informed consent, first cohort of 26 cases were managed with 100µg of misoprostol inserted in posterior fornix every four hourly (maximum 600µg in 24 hours).

Subsequently, second cohort of 26 women was managed using following regimen. The women received a single dose of 200mg mifepristone orally, following which a 24-hour-interval was recommended before administration of misoprostol. After 24 hour, 100µg of misoprostol was inserted into the posterior vaginal fornix by a resident doctor. Following administration of the first dose, a further four doses of misoprostol 100µg were given per vaginum every four hourly if required. Although 24 hours was recommended, but misoprostol inserted in 3 cases earlier as mild bleeding started before 24 hours. Subsequent to misoprostol administration, uterine contractions, pulse, blood pressure, temperature and systemic symptoms were monitored hourly. Oxytocin was used for augmentation of labor in active labor if required. Cases having hyperthermia more than 100 degree Fahrenheit were treated with paracetamol. Analgesic as per patient's requirement orally or parentral pentazocine (50 mg) maximum every six hours was administrated.

Results

Obstetrical parameters of both groups were comparable with no significant difference. Patient characteristics and obstetric parameters are shown in table 1. Efficacy of combined regimen was compared by following parameter. The induction to delivery interval reflects the time interval between first-dose of misoprostol to expulsion of the fetus. Dose of misoprostol required were compared between two groups (tables 2 and 3). Induction to delivery interval ranging from 4-14 hours in mifepristone plus misoprostol group was compared to induction to delivery interval ranging from11 -22 hours in misoprostol group.

Table 1: Age, parity and period of gestation of subject studied

	Age in years (mean ±S.D)	Parity (mean ±S.D)	POG in Weeks (mean ±S.D)
Combination Group (n=26)	27.9 ±4.6 years	2±1.2	34.63±1.1week
Misoprostol Group (n=26)	26.8±6.6 years	2.4±1.4	35± 0.9weeks
P value	Not significant	Not significant	Not significant

POG: period of gestation

Table 2: Comparison of efficacy of both regimens

Study Group	Induction to delivery interval (mean ± S.D) in hours	No. of dose of misoprostol (mean ± S.D)
Combination Group	8.46±3.03	1.69±.73
Misoprostol group	15± 4.14	3.2±1.16
P value	<0.001	< 0.001

Table 3: Safety and tolerance of both regimens were compared in following parameter

Study parameter	Combined regimen group	Misoprostol group
No cases required analgesia	46 %(oral) 19.26% (parental)	65.38%(oral) 23.07% (parental)
Oxytocin required	0	3(11.5%)
Adverse effect	2(7.6%)	2(7.6%)
PPH	0	1(3.8%)
Retained placenta	1(3.8%)	3(11.5%)

Nausea, vomiting, diarrhea and hyperthermia were recorded as adverse effects.

No cases of uterine tachysystole, hypertonicity, hemorrhage or coagulopathy were recorded in any groups .only one cases of postpartum hemorrhage (PPH) was seen in misoprostol group. Augmentation of labor with oxytocin was required in 3 cases, but no oxytocin was required in combination group.

Discussion

Misoprostol doses regimen varied in different studies, we used dose regimen given by World Health Organization (WHO) for induction of IUFD cases after 26 weeks of gestation. Induction delivery interval depends on parity and period of gestation, but confounding effect of these can be ruled out as both groups was comparable in these parameters. As clearly evident from the study results that mifepristone and misoprostol combination had shorter induction delivery interval. This is in agreement with study done by Wagaarachchi et al. (2002) and Varynen et al. (2007) (3, 4).

Dose of misoprostol required was significantly higher in misoprostol group which can be explained on the basis pharmacodynamics of mifepristione as mentioned earlier.

More cases required analgesia in misoprostol group as compared to combination group which can be directly correlated with length of contraction or duration of labor. Although there is possibility of confounding factor of patient's perception of pain, we decided to give analgesia as per patient's need not as routine protocol.

Incident rate of retained placenta was 11.5% in misporostol group as compared to 3.8% in combination group. of Incident rate of retained placenta in misoprostol group was in agreement with earlier study St done by De Heus R et al (5).

Although we preferred to keep all patient admitted in hospital after administration of mifepristone for observation, no adverse event was found. Only in 3 cases mild bleeding started between 18 and 20 hours, so patient could spend this time at home with proper counseling.

Conclusion

In intrauterine fetal death case, mifepristone plus misoprostol is an effective regimen to cut short the fruitless journey of labor pain. It is equally safe, easily, tolerable, and more efficacious than conventional regimen of misoprostol alone.

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References

1. Newhall EP, Winikoff B. Abortion with mifepristone and misoprostol: regimens, efficacy, acceptability and future directions. Am J Obstet Gynecol 2000;183:S44-53.
2. El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Inductionof abortion with mifepristone (RU 486) and oral or vaginal misoprostol. N Engl J Med 1995;332:983–7.
3. Wagaarachchi PT, Ashok PW, Narvekar NN, Smith NC, Templeton A. Medical management of late intrauterine death using a combination of mifepristone and misoprostol. BJOG 2002;109:443-7.
4. Vayrynen W, Heikinheimo O, Nuutila M. Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. Acta Obstetriciaet Gynecologica Scandinavica 2007;86: 701–5.
5. De Heus R, Graziosi G, Christiaens G, Bruinse H, Mol B. Medical management for termination of second and third trimester pregnancies : a comparison strategies. Eur J Obstet Gynecol Reprod Biol 2004; 116: 16-21.