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Comparison between Vaginal and Oral Misoprostol for the Induction of Labour in Patients with Intrauterine Fetal Death

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ABSTRACT

Background & objective: A woman may need to give birth prior to the spontaneous onset of labour in situations where the fetus has died in utero or for the termination of pregnancy where the fetus, if born alive would not survive or would have a permanent handicap. Misoprostol is a prostaglandin medication that can be used to induce labour in these situations. But there is widespread dispute as to which route of administration to be preferred in terms of efficacy and safety. The present study was intended to compare the oral and vaginal misoprostol in the termination of pregnancy with intrauterine foetal death (IUFD).

Methods: This randomized clinical trial (RCT) was carried out in the Department of Obstetrics & Gynecology, Rajshahi Medical College & Hospital (RMCH) over a period of 12 months from July 2018 to June 2019. Pregnant women with established IUFD after 28 weeks of gestation were the study population. A total of 108 such patients were included in the study and were randomly and equally allocated into Oral Misoprostol (OM) and Vaginal Misoprostol (VM) Groups to receive either tablet misoprostol 100 µg orally or tablet misoprostol 100 µg via vaginal route. The outcome measures were successful delivery within 24 hours following induction, induction to delivery interval and induction to pain interval. The maternal safety was evaluated in terms of incidences of side-effects and complications.

Result: In the present study all cases of IUFD delivered successfully and there was no case of failed induction. The comparative evaluation between oral and vaginal misoprostol in the management of IUFD demonstrated that the induction to delivery interval and induction to labour pain interval both were significantly lower in VM Group than those in OM Group ($p < 0.001$ and $p < 0.001$ respectively). The amount of misoprostol needed was also lower in the former group than that in the latter group ($p < 0.001$). The incidence of side-effects like nausea was significantly lower in VM Group than that in OM Group ($p = 0.001$), while vomiting was completely absent in the VM group ($p = 0.013$). There was no incidence of pyrexia in the VM Group.

Conclusion: The study concluded that oral misoprostol for induction of labour for termination of pregnancy in the third trimesters following IUFD is comparatively less effective than vaginal misoprostol, with women experiencing a longer induction to birth interval. The incidence of side-effects (nausea, vomiting and pyrexia) is also more in the oral misoprostol group.

Key words: Vaginal and oral misoprostol, induction of labour, intrauterine fetal death etc.

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INTRODUCTION:

Pregnancy loss at any stage is emotionally distressing, and can be even more so at advanced gestations of more than 24 weeks when the fetus is deemed legally viable.[1] Worldwide about 2.6 million intrauterine fetal death (IUD) occurs (almost 1 for every 45 births), particularly in the developing world (South Asia and Africa). There are several causes of IUDs, such as pre-eclampsia and birth complications, problems with the placenta or umbilical cord, birth defects, infections such as malaria and syphilis, and poor health of the mother. Risk factors include a mother's age over 35, smoking, drug use, use of assisted reproductive technology & first pregnancy.[2] Intrauterine fetal death may be suspected when no fetal movement is felt and is confirmed by ultrasound. Usually, labour begins spontaneously after two weeks, so that women may choose to wait and bear the fetal remains vaginally.[3] But this can be associated with emotional distress, intrauterine infection if the membranes are ruptured, and if there is time-related risk of consumptive coagulopathy. That's why medical induction is recommended to expel the dead fetus.

Most common methods of induction are amniotomy, mechanical dilatation with a balloon catheter, pharmacological inductions with prostaglandin E1 (misoprostol), prostaglandin E2 (dinoproston), or oxytocin.[4] Misoprostol has been the agent of choice for pre-induction cervical ripening for several decades and is one of the pharmacologic agents approved by the United States Food & Drug Administration for this indication. Misoprostol is a synthetic analogue of the prostaglandin E1 that entered the global market in the late 1980s and was originally produced for the prevention of gastrointestinal ulcers. Later, it has been found to be a useful drug with a wide range of applications in both obstetrics and gynaecology. It was first used in 1987 for induction of labour in a dead foetus.[5] Misoprostol increases myometrial contraction as well as decreases cervical resistance. It could be given orally, sublingually or vaginally in doses ranging from 100 to 800 micrograms.[6]

The advantages of the oral route include ease of administration and the ability to administer repeated doses without internal examinations and without increasing the risk of bacterial contamination in women with ruptured membranes. In case of vaginal route, misoprostol shows in slower increase and lower peak plasma concentration and uncomfortable to administration,[7] but the systemic bioavailability has been found to be three times higher as compared to oral administration.[8] But several problems have been identified with vaginal misoprostol like inconsistent and incomplete absorption of the tablet even after several hours of administration. Moreover, women consider vaginal administration uncomfortable. The advantages of the oral route include ease of administration and the ability to administer repeated doses without internal examinations and without increasing the risk of bacterial contamination in women with ruptured membranes. However, systemic side effects (shivering, diarrhoea, vomiting & pyrexia) are more common with oral misoprostol (44.5%) compared to vaginal misoprostol (20%).[9] Thus, the most suitable route for induction of IUFD is not yet clear.[10.11] That purpose the present study was done to compare the efficacy and safety of oral versus vaginal misoprostol for the induction of labour in women with IUFD.

METHODS:

Having obtained ethical clearance from the Ethical Committee of Rajshahi Medical College (RMCH), Rajshahi, this randomized clinical controlled trial (RCT) was conducted in the Department of Obstetrics & Gynecology, RMCH over a period of 12 months from July 2018 to June 2019. Adult pregnant women with confirmed intrauterine fetal death (IUFD) (by Ultrasongoram) having > 28 weeks of gestation, singleton pregnancy & longitudinal lie were included in the study. Transverse lie, foetal macrosomia, previous uterine scar, placenta previa, or any contraindications to receiving prostaglandin were excluded from the study. A total of 108 women who met the above-mentioned eligibility criteria were included. Then all the women were counseled regarding induction & options available for induction. All merits and demerits of induction methods, complications and side-effects of medicine used were explained to them. Consent was taken from the patients after counseling them.

The participants were then randomly assigned to

either of the two regimens (so that every patient had an equal chance to receive either of the regimens) to receive either tablet misoprostol 100 µg orally or tablet misoprostol 100 µg via vaginal route. The women who received oral misoprostol were designated as OM Group (n = 54) and those who received vaginal misoprostol were termed as VM Group (n = 54). While women in OM Group received 100 µg of oral misoprostol, repeated every six hours for a maximum of four doses, women in VM Group received 100 µg of misoprostol intravaginally into posterior fornix and the dose was repeated six hourly up to a maximum of four doses. Women in OM Group swallowed the pills with sips of water in presence of the investigator. In VM Group vaginal cleansing was performed with 10% povidone iodine before insertion. Following insertion, women were advised to remain in fully recumbent position for three hours.

All patients were monitored for pulse, blood pressure, temperature, lower abdominal pain, bleeding and for the development of any side effects. The women were requested to inform the investigator if they experienced any side-effects like fever or shivering. Both groups were assessed for following outcome measures: complications (retained placenta, postpartum hemorrhage), side effects (nausea, vomiting, hyperstimulation, tachysystole, diarrhoea, shivering, pyrexia), induction-to-delivery time and induction-to-pain interval. Moreover, total number of required doses to complete the procedure were also recorded on data collection sheet. Collected data were processed and analyzed using SPSS (Statistical Package for Social Science), version 23.0. Continuous data were expressed as means ± standard deviations (SD) and categorical data were expressed as frequency and percentage. While continuous data were analyzed and compared between groups using Student's t-Test, categorical data were compared between groups using Chi-square (χ^2) or Fisher's Exact Probability Test as the data demanded. For all analytical tests, the level of significance was set at 5% and p-value < 0.05 was considered significant.

RESULTS:

Age distribution between groups showed that the mean ages of the study groups were almost similar (p= 0.255). The housewives were predominant in both groups with no significant intergroup difference (p=0.567). The oral and vaginal misoprostol groups were almost homogeneous in terms of gestational age (p=0.455). The distribution of parity was also no different between the groups (p=0.445). The mean age of the last child was almost similar between the study groups (p=0.336) (Table I). None of the clinical characteristics (anaemia, oedema and fever) were any different between the groups (p=0.661, p=0.135 and p=0.248 respectively). However, mean systolic blood pressure was significantly higher in the OM Group than that in VM Group (p = 0.025) (Table II). The initial Bishop's score was considerably high in the OM Group than that in the VM Group (p=0.267). The induction to delivery and induction to pain intervals both were significantly higher in OM Group than those in VM Group (p< 0.001 and p< 0.001 respectively). The mean number of misoprostol doses was lower in the former group than that in the latter group (p<0.001) (Table III).

Table I. Distribution of demographic and obstetric characteristics between groups

Demographic & obstetric characteristics	Group		p-value
	OM-Group (n = 54)	VM-Group (n = 54)	
Age* (yrs)	26.7 ± 6.0	28.1 ± 6.7	0.255
Occupation#			
Housewife	46(85.2)	48(88.9)	
Working mother	8(14.8)	6(11.1)	0.567
Gestational Age* (weeks)	35.3 ± 3.6	35.9 ± 4.0	0.455
Parity#			
Nulipara	20(37.0)	20(37.0)	
Primipara	30(55.6)	26(48.1)	0.445
Multipara	4(7.4)	8(14.8)	
Age of the last child* (yrs)	5.8 ± 1.8	6.3 ± 2.1	0.336

Figures in the parentheses denote corresponding **percentage.**
* Data were analyzed using **unpaired t-Test** and were presented as **mean ± SD.** #Data were analyzed using **Chi-square** (χ^2).

Table II. Comparison of clinical characteristics between groups

Clinical characteristics	Group		p-value
	OM-Group (n = 54)	VM-Group (n = 54)	
Anaemia#	13(24.1)	15(27.8)	0.661
Oedema#	6(11.1)	2(3.7)	0.135
Fever#	0(0.0)	2(3.7)	0.248
Systolic BP*	114.3 ± 20.8	105.7 ± 17.8	0.025
Diastolic BP*	71.5 ± 17.3	66.7 ± 15.8	0.134

*Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD**
#Data were analyzed using **Chi-square** (χ^2) **Test.**

Table III. Comparison of outcome between the study groups

Outcome variables*	Group		p-value
	OM-Group (n = 54)	VM-Group (n = 54)	
Initial Bishop's score	5.1 ± 1.0	5.8 ± 1.3	0.267
Induction to delivery interval (hrs)	20.5 ± 6.7	14.5 ± 5.2	< 0.001
Induction to pain interval (hrs)	5.9 ± 3.4	3.3 ± 1.8	< 0.001
Number of doses required	2.6 ± 0.7	1.5 ± 0.7	< 0.001

*Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD**

The incidence of side-effects like nausea was significantly lower in VM Group than that in OM Group (p=0.001), while vomiting was completely absent in VM Group (p=0.013). There was no significant difference between the study groups in terms of hyperstimulation and shivering (p=0.495 & p=0.567 respectively). None of subjects in VM Group developed pyrexia, while 4(7.4%) cases in OM Group developed it (p=0.059) (table IV). Comparison of complications encountered by the patients between groups revealed that the incidences of retained placenta and PPH were much lower in VM Group than those in OM Group, although the difference did not turn to significant (p=0.135 and p=0.279 respectively) (Table V).

Table IV. Comparison of side-effects between the study groups

Incidence of side-effects	Group		p-value
	OM-Group (n = 54)	VM-Group (n = 54)	
Nausea#	18(33.3)	4(7.4)	0.001
Vomiting*	6(11.1)	0(0.0)	0.013
Hyperstimulation*	2(3.7)	0(0.0)	0.495
Shivering#	8(14.8)	6(11.1)	0.567
Pyrexia*	4(7.4)	0(0.0)	0.059

*Data were analyzed using **Fisher's Exact Test**; #data were analyzed using **Chi-square (χ^2) Test**

Table V. Comparison of complications between groups

Complications	Group		p-value
	OM-Group (n = 54)	VM-Group (n = 54)	
Retained placenta*	6(11.1)	2(3.7)	0.135
PPH#	10(18.5)	6(11.1)	0.279

*Data were analyzed using **Fisher's Exact Test**; #data were analyzed using **Chi-square (χ^2) Test**

DISCUSSION:

When a foetus dies in the uterus, the options for health care are either spontaneous labour or induce labour.[3] In cases where expectant management is chosen, the clinical concern will be the development of disseminated intravascular coagulation with its inherent risks of haemorrhage, blood product transfusion and maternal death. So, induction remains the second option and it is the evidence-based practice in obstetrics. In cases of IUFD, therefore, the decision to induce labour in a patient with ripen cervix is straightforward and the procedure is often uncomplicated. However, there is no "Gold standard" treatment (either medical or surgical) for late IUFDs.

In the present study, all cases of IUFD were delivered successfully and there was no case of failed induction. The comparative evaluation between oral and vaginal misoprostol in the management of IUFD demonstrated that the induction to delivery interval and the induction to labour pain interval both were significantly lower in VM Group than those in OM Group ($p < 0.001$ and $p < 0.001$ respectively). The amount of misoprostol needed was also lower in VM Group than that in OM Group ($p < 0.001$). The incidence of side-effects like nausea was significantly lower in the former group than that in the latter group ($p = 0.001$), while vomiting was completely absent in the VM group ($p = 0.013$). There was no incidence of pyrexia in the VM Group. As all the baseline characteristics like age, gestational age, gravida and clinical characteristics of the mothers like anaemia were almost identically distributed between groups, the outcome obtained could be attributed to intervention. Nyende[12] compared the effects of oral misoprostol 200 micrograms with vaginal misoprostol 200 micrograms, at 6-hourly interval up to four doses, in women with IUFD after a mean gestation of 29 weeks. Consistent with the findings of the present study, they found that vaginal misoprostol group were significantly more likely to have shorter induction-to-birth time than oral misoprostol group (14 hours versus 21 hours respectively) and less likely to need oxytocin augmentation (20% versus 56% respectively). The vaginal misoprostol group was also less likely to experience gastrointestinal side effects (20% versus 45%, $p < 0.05$). Another study reported that misoprostol is effective and safe for induction of labor in case of second or third trimester fetal death or termination of pregnancy. But

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compared to oral route, vaginal route reduces the induction-expulsion time. The rate of undelivered patients in the first 24 hours is also reduced without increasing side-effects in patients receiving misoprostol intravaginally.[13]

A meta-analysis[14] (which included 3679 women in 38 studies) showed that the use of vaginal misoprostol in the termination of second and third trimester of pregnancy is as effective as other prostaglandin preparations (including cervagem, prostaglandin E2 and prostaglandin F2), and more effective than oral misoprostol. There were no statistically significant differences for the other outcomes reported including need for analgesia, surgical evacuation of the uterus, and side effects including nausea, vomiting, diarrhoea and pyrexia.[14] In another meta-analysis, there were 75 trials (13,793 women) of mixed quality. In nine trials comparing oral misoprostol with placebo (1109 women), women using oral misoprostol were more likely to give birth vaginally within 24 hours and less likely to undergo caesarean birth. Differences in uterine hyperstimulation with fetal heart rate changes were compatible with no effect. Ten trials compared oral misoprostol with vaginal prostaglandin (dinoprostone) (3,240 women). There was little difference in the frequency of vaginal birth within 24 hours, uterine hyperstimulation with fetal heart rate changes, and caesarean birth. Thirty-seven trials compared oral misoprostol with vaginal misoprostol (6417 women). There was little difference in the frequency of vaginal birth within 24 hours, uterine hyperstimulation with fetal heart rate changes, and caesarean birth. The authors concluded that oral misoprostol as an induction agent is effective at achieving vaginal birth. It is more effective than placebo, as effective as vaginal misoprostol and vaginal dinoprostone, and results in fewer caesarean sections than oxytocin alone.[15] Sharply contrasting to these findings, a study from Thailand reported a significantly shorter mean induction-to-birth time in oral misoprostol group compared to that in vaginal misoprostol group (14 versus 19 hours, $p < 0.001$). The success in induction at 24 hours was also significantly higher in the oral misoprostol group (93% versus 68%, $p < 0.001$). All women delivered within 48 hours and subgroup analyses did not show any significant differences in the mean induction-to-birth time between the 16–22 weeks and over 28 weeks gestational age groups using either oral or vaginal misoprostol. However, the mean induction-to-birth time in 23–28 weeks group differed significantly, favouring oral misoprostol (14 versus 20 hours, $p = 0.027$). Significantly more women in the oral group reported diarrhoea. However, other effects (nausea, vomiting, fever, postpartum haemorrhage and analgesia) were similar between the two treatment groups.[16]

CONCLUSION:

From the findings of the present study and discussion thereof, the use of oral misoprostol for induction of labour for termination in the second and third trimesters of pregnancy following intrauterine fetal demise, is less effective than vaginal misoprostol, with women experiencing a longer induction to birth interval. However, important information regarding maternal safety, and in particular the occurrence of rare outcomes such as uterine rupture, remains limited. Future research efforts should be directed towards determining the optimal dose and frequency of administration, with particular attention to standardized reporting of all relevant outcomes and assessment of rare adverse events.

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