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ORIGINAL PAPER

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COMPARISON BETWEEN SUBLINGUAL AND VAGINAL ROUTE OF MISOPROSTOL IN MANAGEMENT OF FIRST TRIMESTER MISCARRIAGE MISSING

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ABSTRACT

Background: Each year, more than forty million abortions are occurred whole of the world. Misoprostol is a prostaglandin analogue with a strong uterotonic effect. The present study aimed to compare the efficacy of Misoprostol in first trimester abortion through two sublingual and vaginal routes of administration. **Methods:** This randomized clinical trial was conducted on 52 consecutive women in first trimester candidate for pregnancy termination because of fetal IUFD or missed abortion in sonography reports. The patients were hospitalized and then randomly assigned to receive sublingual Misoprostol (400 µg, n = 27) or vaginal Misoprostol (400 µg placed in posterior fornix, n = 25). **Findings:** None of the pregnant in the sublingual group developed complete abortion at the end of follow-up time, while 36% of women inducted with vaginal misoprostol experienced complete abortion indicating a intergroup significant difference ($p = 0.001$). Compared with vaginal group, those women in sublingual group experienced more complications including diarrhea (22.2% versus 0.0%), nausea and vomiting (22.2% versus 0.0%), and abdominal pain (3.7% versus 0.0%). **Conclusion:** The use of Misoprostol in vaginal route results in more abortion completeness as well as lower complication rate as compared to sublingual prescription of the drug.

Key words: Sublingual, Vaginal route, Misoprostol, Abortion, Pregnancy termination.**1. INTRODUCTION**

Each year, more than forty million abortions are occurred whole of the world (1). Most of the inducible abortions are performed by surgical methods as the gold choice procedure however may lead patients' dissatisfaction and post-operative serious complications (2). By advancing medical services as alternative methods for performing abortion, this modality has replaced previous surgical methods especially for abortions occurring within first trimester (3). In the early 1970s, a first generations of pregnancy terminating medications consisting prostaglandins was introduced that followed by developing drugs consisting anti-progesterone in 1980 (4). By developing these alternatives particularly drugs including prostaglandins, some large trials could demonstrate their efficacies with high successfulness for inducing abortions during first trimesters (5). The most important effect of prostaglandins is uterine contractions and ripening the cervix.

Misoprostol is a prostaglandin analogue with a strong uterotonic effect (6). This drug has a wide clinical applications including prevention of peptic ulcer induced by non-steroidal anti-inflammatory drugs and also of its serious complications such as gastric bleeding (7). This drug is now widely used for inducing pregnancy terminations that its complete abortion rate has been reported between 61% and 93% (8). The effectiveness of this drug is dependent to the dose of usage, following its repeated dose as well as it using in combination with other drugs such as methotrexate that led to a complete abortion rate of 98% (9, 10).

Despite Misoprostol can be used with different roots including oral, sublingual and vaginal, however a few evidences are available in drug effectiveness as well as its related side effects when use in different roots. Hence, the present study aimed to compare the efficacy of Misoprostol in first trimester abortion through two sublingual and vaginal routes of administration.

2. METHODOLOGY

This randomized clinical trial was conducted from April 2014 to November 2014 on 52 consecutive women in first trimester admitted to Amiralmomenin hospital in Zabol city that were candidate for pregnancy termination because of fetal IUFD or missed abortion in sonography reports. Those women with previous scar on uterine were excluded from the study. Patients with external and internal opening of the cervix is open to both symptoms of abortion is spontaneous start of the study were excluded. All patients were hospitalized and then randomly assigned to receive sublingual Misoprostol (400 µg, n = 27) or vaginal Misoprostol (400 µg placed in posterior fornix, n = 25). Because of small sample size, block randomization was performed according to the time of admission. Single blind allocation and intervention were conducted by a nurse working in the midwifery unit. One of women in first group had history of thyroid nodule that was treated with levothyroxine. One patient in another group had history of PIH in her previous pregnancy. The study was approved by Institutional Ethics Committee, the patients and the attendants were explained about the procedure and informed consent was obtained. On admission, a complete medical history was obtained from all subjects and all were physically examined and vital sign were checked and monitored every 4 hours. The presence or absence of vaginal bleeding presence or absence of uterine contractions that indicate the pain was identified in all patients. The external opening of the cervix, both domestic as well as those that were open were signs of spontaneous abortion is excluded. The initial dose repeated every 4 hours to termination of pregnancy or maximum dose of 2000 microgram. The abortion was then induced in all women. The main criterion for effective medical abortion was considered occurring abortion within 24 hours after induction. After inducing abortion, all women were reassessed by sonography. Complete abortion was defined as complete expulsion of the pregnancy products or endometrial diameter less than 10 mm and absence of residue in sonographic report, otherwise it was considered as incomplete abortion. The study end points were completeness of abortion and also tolerability and complications of the used regimens.

Frequencies of different clinical and demographic variables between patients receiving two treatment methods were compared by Chi square and fisher exact tests (for categorical variables) and Mann Whitney test (for continues variables). Association between these methods and experiencing complete abortion was assessed using multivariate Cox regression models. P value less than 0.05 was considered significant. All analyses were performed using STATA v.11 software.

3. RESULTS

In sublingual group, one of the subjects did not respond to medical abortion that underwent curettage surgery and was thus excluded. Another one had severe abdominal pain that was also excluded because on intolerability. Thus, 27 women in vaginal group and 25 women in sublingual group were included in further assessment. The overall mean age was 30.48 ± 6.07 years (29.48 ± 6.21 years in vaginal group and 31.56 ± 5.85 years in Sublingual group, $p = 0.221$). Mean

Characteristics	Sublingual group (n = 27)	Vaginal group (n = 25)	P-value
Incomplete abortion	27 (100)	16 (64.0)	0.001
Complications	13(48.1)	5(20)	0.03
Parity > 4	8 (29.63)	5 (20.0)	0.30
Pain(uterine contraction)	4 (14.81)	5 (20.0)	0.41
Vaginal bleeding	11 (40.74)	11 (44.0)	0.55

Table 1. Clinical characteristics of pregnant women induced with sublingual or vaginal Misoprostol

time of follow-up for women prescribed with sublingual and vaginal inducers were 570 ± 217 min and 514 ± 208 min respectively with no difference between the groups ($p = 0.6$). As illustrated in Table 1, none of the pregnant in the sublingual group developed complete abortion at the end of follow-up time, while 36% of women induced with vaginal misoprostol experienced complete abortion indicating a intergroup significant difference ($p = 0.001$). Compared with vaginal group, those women in sublingual group experienced more complications including diarrhea (22.2% versus 20.0%), nausea and vomiting (22.2% versus 0.0%), and abdominal pain (3.7% versus 0.0%). According to the patient to increase the frequency of bowel movements, diarrhea, loose stool consistency have been reported.

4. DISCUSSION

Some previous reports comparing efficacy of different roots of Misoprostol on abortion completeness showed similar drug efficacy when administrated vaginally or sublingually, however some others confirmed the superiority of one prescribing protocol compared with another. In a similar study by Parveen et al in 2011, the average time for cervical ripening was significantly less in sublingual administration as compared to the vaginal rout. Also, although the intra-operative pain severity of the sublingual group was lower in comparison to the vaginal route, loose motions and nausea/vomiting were more prevalent in sublingual group than in vaginal group. Vimala et al (11) indicated that the duration of the procedure and the amount of blood loss were similar in the two groups prescribed vaginal and sublingual Misoprostol whereas those women in the sublingual group experienced significantly more shivering and preoperative vaginal bleeding. Interestingly, Tanha (12) and colleagues found that although the effectiveness was high in the sublingual group than in vaginal group, the sublingual group experienced more prevalence rate of bleeding, pain severity, diarrhea and fever. Also, Ganguly et al (13) showed that the rate of complete abortion was higher in sublingual group in comparison to vaginal route, surgical evacuation was required in less number of cases in sublingual group, induction-abortion interval was least with the sublingual route, however gastro-intestinal side-effects more prevalent in sublingual rout. In another study by Saxena et al (14), sublingual group had a higher dilatation and lower time duration of surgery as compared to vaginal routes. Furthermore, pain severity in the sublingual group was significantly lower and patient acceptability was higher for sublingual as compared to vaginal route. As shown in various reports, contradictory results have been revealed regarding more efficacy, tolerability, as well as complications of the different administration routs including sublingual

and vaginal routes. Although we could show lower efficacy as well as higher complications of sublingual versus vaginal prescription of Misoprostol, some pointed studies obtained higher efficacy and lower rate of complications by administering Misoprostol as sublingually when compared with its using orally. In all reviewed studies, the doses of administrated drugs were similar and thus different dosages could not be a potential confounder explaining these heterogeneities. However, some other factors such as differences in exclusion criteria, study sample sizes, or main characteristics of clinical trials such as method of randomization may affect the results and thus power of the studies. It can be suggested that although use of sublingual Misoprostol is prefer for women candidates for terminating pregnancy because of the ease of use, but it's probable lower efficacy and also higher gastrointestinal side effects should not be also ignored. In contrast, vaginal use of drug may result in some specific complications such as vaginal bleeding as shown in some studies and also may cause high patients' dissatisfaction. It seems that the selection of the route of administration should be considered based on the physician discretion and patient clinical condition. However, due to higher rate of abortion incompleteness and higher complication rates in sublingual group shown in our study, higher caution should be considered in the use of sublingual route.

Fateen et al showed the use of sublingual misoprostol to induce cervical priming in first trimester abortion was efficient and as effective as vaginal misoprostol with more convenience to the patient and avoided the need of the doctor to insert it (15). Shah et al demonstrated Sublingual and vaginal misoprostol are both equally effective for the medical management of missed miscarriage although their overall effectiveness is low within the first 24 hours. Sublingual misoprostol is associated with more side effects especially an unpleasant taste (6). Sublingual and vaginal misoprostol are both equally effective for the medical management of missed miscarriage although their overall effectiveness is low within the first 24 hours. Sublingual misoprostol is associated with more side effects especially an unpleasant taste.

Parveen et al. concluded that sublingual misoprostol is an effective and favorable cervical ripening agent for first trimester abortion as compared to vaginal and oral dosage forms (17). Some limitations included in this research; Lack of willingness of patients to choose medical approach of treatment as it is very slow in comparison with the surgery. Additionally the patients with scar on uterus has been omitted from study. If the dose of treatment was less, it might include them in this study. The third limitation was indexing patients with diarrhea only based on their report and we did not measure the volume of stool as a factor. Therefore this may include error because patients may reported based on number of times going to toilet and loose stool consistency.

5. CONCLUSION

In conclusion, according to our findings, the use of Misoprostol in vaginal route is more abortion completeness as well as lower complication rate as compared to sublingual prescription of the dru/g. In this regard, the use of Misoprostol vaginally should be more scheduled because may lead higher patients' satisfaction.

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- **Conflict of interest:** The authors report no conflict of interest related to this paper.

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