COMPARATIVE STUDY BETWEEN VAGINAL AND SUBLINGUAL MISOPROSTOL IN THE MANAGEMENT OF FIRST TRIMESTER SILENT MISCARRIAGES

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ABSTRACT

Background

Surgical evacuation is the traditional method for termination of first trimester silent (missed) miscarriage. But serious complications may occur after surgical evacuation e.g. perforation, bleeding infection and later infertility. Now a day medical termination of first trimester silent miscarriage is well recognized as an effective treatment option. Misoprostol tablet is a drug which can be used & it has been found to be effective by different routes; orally, vaginally & sublingually.

Objective

This study was conducted to evaluate the effectiveness of sublingual versus vaginal misoprostol in the management of first trimester silent miscarriage.

Patients and Methods

This is a prospective randomized comparative clinical study, included pregnant women who have first trimester silent miscarriage, attending Sulaimani Maternity Teaching Hospital over a period of 8 months (from 1st January 2009 till 1st September 2009). These pregnant women were divided into two groups as follow: **Group 1** included 44 patients, who received 600µg (3 tablets) of Misoprostol sublingually, every 3 h for a maximum of 3 doses. **Group 2** included 44 patients, who received 600µg (3 tablets) of Misoprostol vaginally every 3 hr for a maximum of 3 doses. These women were followed up for 24 hr to see whether they pass any product of conception or not, if no abortion takes place, the women were given a second course of treatment, and followed up for another 24 hr to see the results.

Results

All the women included in the study (no= 88) passed product of conceptions after receiving the first course of the treatment .The complete abortion rate was significantly higher in sublingual group 22 (50%) compared to vaginal group 6 (13.63%), (p=0.000).The mean time interval between induction to passage of product of conception was significantly shorter in sublingual group (6.68 h) compared to vaginal group (8.61 h), (p<0.002). No significant difference in the incidence of side effects was observed in both groups.

Conclusion

This study shows that sublingual misoprostol was more effective than vaginal misoprostol in inducing complete abortion for silent miscarriage in the first trimester, with no significant difference in the side effects.

Keywords: *First trimester, Silent miscarriage, Sublingual Misoprostol, Vaginal Misoprostol.*

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INTRODUCTION

Miscarriage is the spontaneous loss of a pregnancy before 22 weeks gestation. Early pregnancy loss is spontaneous loss of a pregnancy before 13 weeks of gestation (1).

Miscarriages occurred in 15-20% of all pregnancies (2). Missed (silent) miscarriage is a gestational sac containing a dead embryo / fetus before 22 weeks of gestation without clinical symptoms of expulsion (2). It is a kind where an embryonic death occurs but the body does not drive out the various elements of a terminated pregnancy. The diagnosis is usually made by failure to identify a fetal heart beat on ultrasound. Within this context the mother often complains of chronic but light vaginal bleeding (1, 3) Management of silent miscarriages includes:

1.Surgical evacuation

The aim is to evacuate the uterus as soon as possible to decrease the risk of infection. The diagnosis of early pregnancy failure is made possible by improvement in ultrasound imaging, which may have resulted in an increase in the number of surgical evacuations performed. (4, 5) If surgical evacuation is to be used, suction curettage is the method of choice as this is associated with fewer complications (6). Serious complications may occur after surgical evacuation including uterine perforation, infection, cervical tears, intrauterine adhesions, hemorrhage and risk of anesthesia, as well as risks of long-term effects on subsequent fertility. The overall complication rate varies between 4-10 %. (4, 5).

2. Medical management

Over the past decade alternative management options (expectant and medical) have been developed and many women prefer the option of treatment without the attendant risks associated with a surgical procedure (7). Several pharmacological agents, capable of inducing abortion, have become available in the last 20 years. Medical termination of pregnancy is now well recognized as an effective treatment option. It was thus a logic progression to use these drugs in the management of miscarriage. Examples of the drugs which can be used to induce abortion are prostaglandins, mifepristone and misoprostol (7).

Misoprostol is a synthetic prostaglandin analogue which is related structurally to naturally occurring prostaglandin E1 (PGE1). PGE1 analogue has long been recognized as an effective inhibitor of gastric acid secretion when administered intravenously and orally; also it is a strong stimulant of the uterus and can be used to terminate pregnancy at different age of gestation (7). Misoprostol is approved in most countries under the brand name Cytotec®. The tablets are produced for oral or vaginal use and contain either 100 or 200 µg of Misoprostol. More recently 25µg tablet for vaginal use has been approved for labour induction. Misoprostol is not expensive, does not require refrigeration and can be given in different dosages by different routes and it is the most commonly used agent in recent published studies (8). Pharmacokinetics: Misoprostol is extensively absorbed and undergoes rapid de-desertification by the liver to form the free acid (Misoprostol acid), which is responsible for its clinical activity (8).

Misoprostol can be administered and it is effective in different routs (oral, vaginal, buccal, rectal and sublingual) (8). It was discovered and proven by clinical studies that vaginal administration is more effective than oral administration in medical abortion (9, 10). In contrast to the oral route, the plasma concentration after vaginal administration increase gradually, reaching maximum level after 70-80 min., it then slowly declines, with detectable level present up to 6 h after administration. Drawbacks of this vaginal administration include the fact that tablets may be found in the vagina during an examination (which may indicate incomplete absorption), also the majority of women prefer the oral route of administration as being more private and convenient (11). The sublingual route was proposed as an alternative to the vaginal route. The Misoprostol tablet can be dissolved in 20 min. when it is placed under the tongue (11). The clinical effect of sublingual Misoprostol administration was investigated in two pilot studies with promising results (11, 12).

A pharmacokinetic study showed that sublingual and oral administration produces the quickest increase in Misoprostol acid when compared with vaginal administration; also sublingual rout can avoid the first pass effect of the oral rout (13).

The aim of this study was to determine the effectiveness of Misoprostol in the medical termination of first trimester silent miscarriage and to compare between sublingual and vaginal Misoprostol in the complete abortion rate.

PATIENTS AND METHODS

This is a prospective randomized controlled clinical trial conducted in Sulaimani Maternity Teaching Hospital, over a period of 8 months (from 1st January 2009 till 1st September 2009). Women included in this study were having first trimester silent miscarriage, attending the Sulaimani Maternity Hospital for termination of their pregnancy. The diagnosis of first trimester silent miscarriage done by ultrasonography.

On admission full history and proper examination and basic investigations were performed to all women in the study. Grandmultiparous women and those with history of more than one previous cesarean section, drug allergy, and those with high risk factors like: (chronic heart diseases, asthma, hypertensions, diabetes and infection) were excluded from the study. The included women were randomized into two groups (randomization done by giving the treatment alternatively that is the 1st women admitted in that day will receive the drug sublingually and the 2nd woman will receive the drug vaginally, then the 3rd sublingually and so on).

Group 1 received 600 µg (3 tablets) Misoprostol sublingually every 3 hours for a maximum of three doses, and group (2) received 600µg (3 tablets) Misoprostol vaginally every 3 h for maximum of three doses. Before randomization all the women were informed about the type of treatment and its side effects and an informed consent was taken. The women in group 1 were instructed to put the three Misoprostol tablets under the tongue themselves under supervision and they were not allowed to have any foods or drinks for the next 20-30 min, in order to allow complete dissolution of the tablets. In group 2, the Misoprostol tablets were put in the posterior fornix of the vagina by the researcher. Oral or parenteral analgesics were given if the women complained of severe pain. The women were kept in hospital for 24 hours and were followed up by the attendant physician to know if they have passed any product of conception (POC) or developed vaginal bleeding. Emergency surgical evacuation was performed if the blood loss or abdominal pain was uncontrolled. If abortion did not occur in the first 24 h, the women were kept for another 24 and were given another course of Misoprostol by the same rout. Pelvic ultrasound was done for those women who had vaginal bleeding or passed product of conception; if the ultrasound examination showed evidence of complete abortion no action was done to them, but if there was significant amount of retained product found in the uterus surgical evacuation was performed. If after completion of two course of Misoprostol, the women did not pass any product of conception they were considered as failure of medical treatment and surgical evacuation was also performed. After abortion women were discharged home, and were asked to come back after 7 days for follow up; at which they were asked about the duration and amount of bleeding after abortion, and if they complained of heavy vaginal bleeding or on previous ultrasound they have mild type of retained POC, a second pelvic ultrasound was done for them, also the PCV level was checked for each women at the follow up visit.

Statistical analysis

Differences in continuous variables were analyzed with student's test for normally distributed data. Differences in discontinuous variables were analyzed by chi-square test. P value <0.05 was considered significant.

RESULTS

Eighty-eight women were included in the study; all were having first trimester silent miscarriage. Forty-four women in each group. Table 1 shows the demographic characteristics of women in group 1 (sublingual group) compared to women in group 2 (vaginal group). There were no significant differences between the two groups with regard to their age, body mass index, parity and gestational age.

All of the women in group 1 and 2 reported passage of POC within the first 24 hours, the complete miscarriage rate was significantly higher in the sublingual group 22 (50%) compared to the vaginal group 6 (13.63%), (p=0.000), as shown in table 2. The mean time interval between inductions to expulsion of POC was shorter in sublingual group (6.68±2.18 hr), compared to vaginal group (8.61±3.46 hr), (P<0.002). The difference is statistically significant, table 3.

There was no significant change in the PCV level before and after abortion in both groups, table 4. The side effects profiles are shown in table 5. The incidence of diarrhea was higher in group 1, (13.63% versus 9.09%), while incidence of nausea and vomiting was higher in group 2. However, the difference in both groups was statistically not significant.

Table 1. Demographic characters of women in both groups

Variable	Group 1*(n=44) Mean ±SD	Group 2** (n=44) Mean ±SD	P value
Age(years)	30.09± 6.7 Range(20-40)	29.43± 6.25 Range(20-40)	0.33
Body mass index	25.3± 2.67	26.50± 2.37	0.06
Gestational age (wk)	7.88± 1.75	8.36± 2.01	0.18
Parity	1.50± 0.236	1.54± 0.209	0.21

*** Group 1, sublingual group. ** Group 2, vaginal group**

Table 2. Complete abortion rate in both groups*.

Clinical outcome	Group 1 (n=44) No (%)	Group 2 (n=44) No (%)	P value
Complete abortion	22 (50%)	6 (13.63%)	0.000
Incomplete abortion	22 (50%)	38 (86.36)	0.000

***The complete abortion rate was significantly higher in group 1, P value< 0.05 considered significant.**

Table 3. The mean time interval between induction and passage of POC in both groups*.

	Group (1) Mean ± SD	Group (2) Mean ± SD	P value
Time between induction and passage of POC in hours	6.6± 2.188	8.6± 3.46	0.002

*** The mean time interval was significantly shorter in group 1.**

Table 4. The level of PCV before and after abortion in both groups*.

Time	PCV value in group 1) Mean ±SD	PCV value in group2 Mean ±SD
Before abortion	36.43± 3.06	35.93± 3.63
After abortion	35.25± 2.48	34.86± 3.9
P value	0.086	0.32

*** No significant difference in PCV value before and after abortion in both groups.**

Table 5. Side effects of Misoprostol in both groups*.

Side effects	Group 1 No (%)	Group 2 No (%)	P value
Diarrhea	6 (13.63%)	4 (9.09%)	0.5
Nausea	0 (0%)	3 (6.81%)	0.08
Vomiting	0 (0%)	1 (2.27%)	0.31
Fever	3 (6.81%)	2 (4.54%)	0.64
Rigor	3 (6.81%)	4 (9.09%)	0.7
Nil	34 (77.27%)	32 (72.72%)	0.62

*** No significant difference in side effects between the two groups.**

DISCUSSION

Misoprostol has been used orally and vaginally for medical abortion and management of miscarriage (9, 14, and 15). Ho *et al*., showed that the vaginal route of administration is more effective and gives a higher complete abortion rate than oral route. However, the oral route is more convenient and acceptable. This is especially true for regimens using Misoprostol alone because repeated administration is required (10). Recently, the sublingual route of administration of Misoprostol has been investigated, this may offer an alternative for women who do not like the vaginal administration of the drug because it is painful and uncomfortable and they prefer drugs that can be taken by mouth. It may be better way of giving the drug in cases of heavy vaginal bleeding, which may affect the absorption in vaginal administration(10). Sublingual Misoprostol is taken by mouth but can avoid the first–pass effect through the liver as in the oral route and therefore may result in a high complete abortion rate (10). Absorption of Misoprostol tablets may be easier to ascertain as the dissolution of the tablets can be easily observed during sublingual compared to vaginal administration, so sublingual Misoprostol is as effective as vaginal Misoprostol and associate with lesser side effects compared to oral Misoprostol (12). Tang *et al*., also showed that sublingual Misoprostol gave the shortest time to peak serum concentration and greatest systemic bioavailability. This means that sublingual Misoprostol may have the most potent and fastest onset of action compared with the other routes of administration. It has been shown that sublingual Misoprostol is as effective as vaginal Misoprostol for the management of silent miscarriage (13). Tang *et al.* showed that the success rate of regimen using 600µg Misoprostol every 3 h for up to 3 doses was 87.5% and it was the same for both vaginal and sublingual routes (12). EI-Rafaey *et al.* showed that the complete abortion rate was 94% in sublingual Misoprostol compared to vaginal Misoprostol (9). In the current study, sublingual Misoprostol gave a higher success rate than vaginal Misoprostol for complete abortion (50% versus 13.63%) and the difference was statistically significant. But the result found to be lower than previous study using same regimen. Ashok *et al.* showed that, the onset of action with sublingual Misoprostol may be faster as the induction to abortion interval was only 2.7 hr, compared to 4 hr, reported in other study using vaginal Misoprostol (16). In this study the induction to abortion interval was also shorter in the sublingual group compared to the vaginal group (6.68±2.18 hr, versus 8.61±3.46 hr). Regarding the incidence of side-effects Tang *et al.*, showed that the incidence of side effects was higher in sublingual administration with a relatively high percentage of women complaining of lower abdominal pain, diarrhea and fever (11).

In this study, higher number of women in the sublingual Misoprostol group, developed diarrhea, while a higher number of women complained of nausea, vomiting and rigor in the vaginal group, but the difference was statistically not significant. Regarding changes in PCV level before and after treatment Tang *et al.*, showed that no any significant change found (12). In this study also the change was statistically not significant.

Conclusions

Sublingual Misoprostol found to be more effective than vaginal Misoprostol in termination of first trimester silent miscarriage with no significant difference in the incidence of side effects.

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