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ORIGINAL ARTICLE

Administration of Misoprostol Sublingual versus Vaginal for the Termination of Second Trimester Missed Miscarriage

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ABSTRACT

Background: miscarriage is the process of fetus extraction (embryo) weighting less than 500 mg equivalent to approximately 20 to 22 weeks gestation. Misoprostol is increasingly used for second trimester termination of pregnancy. It is inexpensive, and it is rapidly absorbed by sublingual, vaginal and oral routes. **Objectives**: This study was carried out for comparing the safety of misoprostol administrated sublingually versus vaginally in the middle of trimester missed miscarriage termination without surgical intervention and with minimum complication. **Patients & Methods:** The study was carried out in high risk unit of Zagazig university and in Whada Derna teaching hospital during the period from April 2017 to January 2018, 32 pregnant women diagnosed as missed miscarriage were divided to 2 groups, **Group A:** Received a dose of 200µg of Misoprostol sublingual and **Group B:** Received a dose of 200µg of Misoprostol vaginally, both each 4 hours up to 6 doses a day. **Results**: there was a high statistical significant differences the two groups according to the means of induction to miscarriage interval. 15 patients in sublingual group and 7 patients in vaginal group miscarriage during 12 hours after treatment. **Conclusion:** Sublingual and vaginal administration of 200 microgram of misoprostol each 4 hours up to 6 doses a day is effective in the second trimester termination in missed miscarriage, sublingual administration is the best choice due to its high response, acceptability, less side effects and great effect, sublingual misoprostol can be self- administrated by patients at home thereby decreasing hospital stay and costs.

Keywords: Misoprostol, Second Trimester, Missed Miscarriage, Sublingual

INTRODUCTION

Missed miscarriage is known as the stop growing or death of the baby without symptoms of miscarriage such as bleeding or pain. Also, it is known as a delayed miscarriage. A missed miscarriage happens when the baby has stopped developing, but the sac remains and body continues to produce hormones that still make women feel pregnant[1].

Miscarriage in second trimester was 10%-15% of the induction miscarriage and cause 2/3 of the serious complication and 50% of the death were recorded in the practice**.** Miscarriage or sudden miscarriage is the end point of pregnancy in which the fetus or embryo can not survive, generally mostly occurs before 20

weeks of gestation. Miscarriage considered an important complication in the early pregnant womens[2].

Most research into the use of misoprostol for the medical discharge of incomplete miscarriage has focused on the effect of oral administration. Recently studies suggested that there would be an improvement in the uterine evacuation and a reduction in side-effects if misoprostol was administered vaginally (3).

Advances in the field of fetal diagnosis showed an increase of second trimester pregnancy terminations. Mifepristone, a progesterone receptor antagonist, considered effective in shortening the miscarriage induction interval when combined with prostaglandins, but it is expensive (4).

Misoprostol is a prostaglandin E_1 analogue that has a small cost, long shelf- life at normal temperature and lower side effects than the prostaglandin E_2 analogue. Misoprostol is the prostaglandin of choice as it also has various administration methods such as vaginal, sublingual and oral. The pregnancy termination in the first trimester using Misoprostol have been studied. many studies have been demonstrated that giving misoprostol vaginally is more better than giving it orally in the pregnancy termination in the first trimester [5].

Recent reports have demonstrated that misoprostol, a synthetic prostaglandin E1 analogue, is a important alternative prostaglandins for its stability at room temperature and wide availability, but its side effects, such as abdominal pain, fever, nausea and vomiting, are still undefined. Efforts to optimize the doses and interval to maximize effectiveness and decrease complications are so important. (6)

Further studies have explored alternate routes of misoprostol administration. Creinin et al. compared complete expulsion rates in women randomized to either 400 mcg oral misoprostol or 800 mcg vaginal misoprostol [7]. Success rates in the oral group was of 25% versus 88% in the vaginal group, which means that vaginal administration is more effective at treating missed miscarriage. However, the use of two different misoprostol doses makes it difficult to conclude that one route is superior to the other. Tang et al.(2003), randomized 80 women to receive 600 mcg misoprostol either vaginally or sublingually. They found an efficacy rate of 87.5% in both groups [8].

AIM OF THE WORK

The aim of this study was to compare the efficacy and safety of misoprostol administrated sublingual versus vaginal for mid trimester missed miscarriage termination without surgical intervention and with minimum complication.

PATIENTS AND METHODS

The study was carried out on 32 pregnant women diagnosed as missed miscarriage admitted to a high risk unit of Zagazig university and in Whada Derna teaching hospital during the period from April 2017 to January 2018, included 32 pregnant women diagnosed as missed miscarriage and estimated gestational age between 13 to 24 weeks and after careful ultrasound examination all of them were informed about the proceedures and possible failures .

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work was carried according to The Code of Ethics of the World Medical Association **(Declaration of Helsinki, 2001)** (9) for studies involving humans

Patients were randomly ditributed into two groups, every group consist of 16 patients.

Group A:

Received a dose of 200µg of Misoprostol sublingual each 4 hours up to 6 doses a day, in case of no response the treatment must be repeated next day. (10)

Group B:

Received a dose of 200µg of Misoprostol vaginally each 4 hours up to 6 doses a day, in

case of no response the treatment must be repeated next day. [10]

Inclusion criteria:

The patients with the following criteria were included in the study :

1. Single pregnancy
2. Sure diagnosis of miscarriage and gestational age according to LMP documented by ultrasonography .
3. Estimated gestational age between 13 to 24 weeks.
4. Age (18 years) and above
5. Normally situated placenta (fundal placenta).

Exclusion criteria:

1) past history for misoprostol contraindication (mitral stenosis, sickle cell anemia, diastolic pressure >100 mmHg, bronchial asthma and glaucoma) uncontrolled seizure disorders, prostaglandins allergy or sensitive to misoprostol .
2)History of thromboembolism.
3)Sever liver disease or hepatic disease
4)Previous uterine scar
5)Low lying placenta.
6)Undiagnosed active vaginal bleeding.
7)Known or suspected extra uterine pregnancy .
8)Multiple pregnancy
9)Known or suspected pelvic infection
10)Cardiovascular disease (valvular disease, angina , arrhythmia and cardiac failure).
11)Adrenal disease

All patients included in our study were subjected to the following:

Complete history was taken, general and local examinations, laboratory investigations (CBC, Rh typing, coagulation profile, liver and renal function tests, viral screening, PTT, urine examinations, fasting blood sugar), trans-vaginal ultrasound pelvic examination .

All patients were followed in the ward every four hours with observation of pulse rate blood pressure temperature and occurrence of side effects before next dose given. Uterine contraction and cervical status were assessed by abdominal and vaginal examination

No additional misoprostol dose was repeated if miscarriage is immenant (patient had at least 70% cervical effacement with 2 cm opening). The induction considered to be started when the patient received the first dose of misoprostol and miscarriage defined as the time when the fetus was expelled (incomplete miscarriage) although in some cases placenta delivered at the same time (complete miscarriage) [11].

After miscarriage ultrasonographic examination was done to confirm that the products of gestation (fetus and placenta) had been successfully removed to establish that the miscarriage was complete. The success was defined as achieving expulsion of products of conception

Statistical analysis

Data were collected, tabulated and analyzed by SPSS 20, software for Windows. The level of significance was set at $P < 0.05$.

RESULTS

Table (1) showed that there was no statistical significant difference between the studied groups regarding body mass index. There was no statistical significant difference between the studied groups regarding the mean maternal age, there was no statistical significant difference between the studied groups regarding the mean gestational age according to last menstrual period ultrasound evaluation and regarding Nulliparous and multiparous there was no statistical significant difference between the studied groups. **Table(2),** showed that there was no statistical significant difference regarding the type of miscarriage between the studied groups. **Table (3),** showed that there was no statistical significant difference according to the number of successful miscarriage within 12 hours after the initial dose administration. **Table (4),** showed that the mean dose of misoprostol required for termination of pregnancy in the sublingual group is significantly less than that required for vaginally treated group with a statistical significant difference. **Table (5),** showed that many adverse effects of misoprostol have been reported, abdominal pain, nausea, vomiting, headache diarrhea, fever, dizziness and severity of bleeding with no statistical significant

difference between the two groups except fever with highly statistical difference. **Table (6),** showed that there was no statistical significant difference between the two groups in the Hb level before and after treatment.

Table (1): Shows comparison between the two groups (sublingual &vaginal groups) in demographic characteristics.

Studied group / Variables	Group (A) sublingual group, N=16	Group (B) vaginal ($\overline{X}$ ±S.D), N=16	P. value	Sig.
BMI($\overline{X}$ ±S.D) (kg/m2)	28 ±3.2	28 ±3.4	0.869	Not sig.
Age ($\overline{X}$ ±S.D) (years)	28 ±5	28 ± 6	0.974	Not sig.
GA($\overline{X}$ ±S.D)(weeks)	17 ±3	16 ±3	0.356	Not sig.
Nulliparous (n&%)	7 (43.75)	6 (37.5)	0.719	Not sig.
Multiparous (n&%)	9 (56.25)	10 (62.5)	0.719	Not sig.

X = mean **S.D = Standard deviation**
GA = gestational age **n = number of cases**
N=sample size **BMI = Body mass index**

Table(2): comparision of type of abortion in sublingual and vaginal groups.

Studied group / Variables	Group (A) sublingual group, N=16	Group (B) vaginal ($\overline{X}$ ±S.D), N=16	P. value	Sig.
Complete Abortion (n & %)	12 (75)	13 (81.25)	0.669	Not sig.
Incomplete Abortion (E&C) (n & %)	4 (25)	3 (18.75)	0.669	Not sig

Table (3): Comparison of abortion within 12 Hours, in sublingual and vaginal groups

Studied group / Variables	Group (A) sublingual group, N=16	Group (B) vaginal ($\overline{X}$ ±S.D), N=16	P. value	Sig.
Abortion within 12 hours (n&%)	15 (93.75)	7 (43.75)	0.002	Sig.
Abortion Within 24 hours (n&%)	16 (100)	16 (100)	P>0.05	Not. sig

Table 4 : comparison the mean dose of misoprostol applied in the sublingual versus the vaginal group.

Variables / Studied group	Group (A) sublingual group N =16	Group (B) Vaginal group N =16	P. value	Sig.
Misoprostol dose, ($\overline{X}$ ±S.D) (µg)	572.5 ± 145.45	675 ± 161.24	0.005	Sig
No of tablets received, ($\overline{X}$ ±S.D)	2.90 ± 0.725	3.38 ± 0.806	0.005	sig

Table 5 : the frequency of side effects in sublingual and vaginal groups

Variables / Studied group	Group (A) sublingual group, N =16	Group (B) vaginal Group, N =16	P. value	Sig.
Nausea (n&%)	10 (62.5)	11 (68.75)	0.710	Not sig.
Vomiting (n&%)	2 (12.5)	3 (18.75)	0.626	Not sig.
Headache (n&%)	9 (56.25)	10 (62.5)	0.719	Not sig.
Diarrhea (n&%)in	2 (12.5)	3 (18.75)	0.626	Not sig.
Abdominal pain (n&%)	12 (75)	14 (87.5)	0.669	Not sig.
Fever (n&%)	1 (6.25)	6 (37.5)	0.04	Sig.
dizziness (n&%)	11 (68.75)	10 (62.5)	0.71	Not sig
Severity of bleeding Less than MP Equal to MP More than MP	 1(6.3) 5(32) 10(62.5)	 2(9.5) 3(19) 11(68.75)	 0.630 0.6 0.710	Not sig

Table 6 : Hb Comparison between sublingual and vaginal groups before and after treatment

Variables / Studied group	Group (A) sublingual group N =16	Group (B) vaginal group N =16	P. value	Sig.
Hb before($\overline{X}$ ±S.D)	10.31 ± 1.22	10.75 ± 1.25	0.687	Not Sig
Hb after ($\overline{X}$ ±S.D)	10.07 ± 1.24	9.89 ± 1.25	0.704	Not Sig

DISCUSSION

In the study of **Tang et al.,** [7] the sublingual and vaginal routes were investigated by administrating a dose of 400 µg misoprostol every 3 hours. The results of this study showed that the success rate through 48 hours and the time of the induction-to- miscarriage interval did not vary significantly between the two methods. However, the success rate through the first 24 hours of the vaginal administration was higher than the sublingual administration, which could be attributed to the local effects of misoprostol in the cervix ripening. This was not in agreement with **our study** (no of miscarriage s within 12 hours was higher in sublingual route than the vaginal but had equal rates within 24 hours) .Vaginal misoprostol remains in the vagina for many

hours after administration but the absorption sometimes incomplete and variable. The reasons may be a consequence of the physical differences within patients, the differences in the bleeding amount from the uterus, the pH of vaginal secretions and the vaginal bleeding can decrease the drug absorption.

In the study of **Ankita Pandey A et al.** [12] who studied the vaginal misoprostol versus sublingual misoprostol administration for second trimester medical termination of pregnancy, they found fever was significantly different between the two groups among the side effects of misoprostol which supports results of **our study** .

In Parallel with **this study**, **Cabrera et al.** [13] who found that the mean duration to miscarriage time in the sublingual method was significantly shorter than the vaginal method

Modak et al. [14] found that the induction miscarriage interval was shorter in sublingual group (12.28 hours), we found the similar results. Subjective assessment of comfort to the route was 88.24% in sublingual group and 54.55% in vaginal group. We also found the patients who took sublingual drug are more comfortable (90%) while the vaginal rout the level of comfort was 60%.High grade fever (>38C) was more in Vaginal group (51.51%) as compared to sublingual group (26.47%) which was in agreement to **our study .**

A study of **Tang et al.** [7] on 18 cases administered misoprostol 200 ug. administered 3-hourly sublingually demonstrated 100% success rate with a mean induction miscarriage interval (12 ± 3.6 hours) which was in agreement to **our study .**

In the study by Tanha et al. [15] who compared a dose of 400μg misoprostol every 6 hours vaginally and sublingually, he reported that there were the similar effects in termination at the second-trimester. The mean induction to miscarriage period was 16 hours that is longer than **our study** (<12 hours) which was may be due to longer interval between drugs application and the sample size difference.

Similar to the study of **Bartusevicius et al.** [16], the present study revealed that induction to miscarriage period in the sublingual group was significantly shorter and needed lower dose of drug for miscarriage. It can be due to different pharmacokinetics profile of two routes.

Some previous studies by **Saxena et al.** [17] and **Tang et al.** [7] suggested that side effects like fever, vomiting , headache, diarrhea, dizzness and abdominal pain were common in each route of administration but this was in contrast to the present study. In the present study, with in agreement with the study made of **Von Hertzen et al.** [17] .

In our study, the patients prefer to use misoprostol sublingually, this finding was in agreement with the studies of **Von Hertzen et al.** [18] and **Bhattacharjeeet al.**[19] in which the patients preferred sublingual misoprostol over its vaginal counterpart .

CONCLUSION

Sublingual and vaginal administration of 200 microgram of misoprostol each 4 hours up to 6 doses a day is effective in the second trimester termination in missed miscarriage, sublingual administration is the best choice due to its high response, acceptability, less side effects and great effect, sublingual misoprostol can be self-administrated by patients at home thereby decreasing hospital stay and costs.

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