



Effectiveness and safety of sublingual misoprostol in medical treatment of the 1st trimester miscarriage: experience of off-label use in Korea

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Objective

This study was conducted to determine the effectiveness and safety of medical treatment with sublingual misoprostol (MS) in the 1st trimester miscarriage under the approval by Health Insurance Review and Assessment Service (HIRA) for off-label usage by the single medical center in Korea.

Methods

A retrospective cohort study was performed in one institution between April 2013 and June 2016. Ninety-one patients diagnosed with miscarriage before 14 weeks of gestation and wanted to try medical treatment were included. A detailed ultrasound scan was performed to confirm the diagnosis. Patients took 600 microgram (mcg) of MS sublingually at initial dose, and repeated the same dose 4–6 hours apart. Successful medical abortion was defined as spontaneous expulsion of gestational products (including gestational sac, embryo, fetus, and placenta). If gestational products were not expelled, surgical evacuation was performed at least 24 hours later from the initial dose. Information about side effects was obtained by medical records.

Results

About two-thirds of patients had a successful outcome. The median interval time from pill to expulsion was 18 hours in the successful medical treatment group. There was no serious systemic side effect or massive vaginal bleeding. Presence or absence of vaginal spotting before diagnosis of miscarriage, uterine leiomyomas, subchorionic hematoma, or distorted shape of gestational sac on ultrasound scan were not statistically different between the two groups.

Conclusion

Medical treatment with sublingual MS can be a proper option for the 1st trimester miscarriage, especially for the patient who want to avoid surgical procedure. We can reduce the unnecessary sedation or surgical intervention in the patients with the 1st trimester miscarriage.

Keywords: Misoprostol; Incomplete abortion; Missed abortion; Spontaneous abortion; Administration, sublingual

Introduction

Miscarriage, also known as missed abortion, is generally defined as spontaneous loss of a previable pregnancy [1]. It complicates 15% to 20% of all pregnancies, 75% of miscarriages occur during the 1st trimester [2-4]. So long as ectopic

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pregnancy is ruled out, almost half of miscarriage get to be expelled spontaneously within two to six weeks [5,6]. However, anxiety of the women diagnosed with miscarriage and symptoms such as vaginal bleeding and abdominal pain usually require prompt interventions for termination of miscarriage [7].

Surgical evacuation using vacuum aspiration or curettage is the most common method for termination of miscarriages [6]. It is widely used because it can achieve complete removal of products of conception in a short time. A kind of anesthesia or sedation is usually necessary during surgical evacuation. However, there are some patients who want to avoid any surgical intervention and prefer non-invasive medical treatment to surgical evacuation. In the western, the combined regimen of mifepristone followed 36–48 hours later by the prostaglandin E1 analogue misoprostol (MS) is generally used for the medical treatment of the 1st trimester abortion with high efficacy and good patient acceptability [8-10]. Medical abortion using the anti-progesterone mifepristone and prostaglandin analogue was approved in France, UK, and Sweden in 1988, 1991, and 1992, respectively. In the USA, mifepristone was approved for medical abortion in 2000 [11]. However, the use of mifepristone for the purpose of medical treatment of the abortion is prohibited in Korea. MS, a synthetic analogue of natural prostaglandin E1, was first marketed in the 1980s to prevent gastric or duodenal ulcer. MS has been used for a long time, also it is inexpensive, easy to be kept at room temperature. MS has additional effect on uterine contractility and cervical ripening, so World Health Organization (WHO) recommended MS for obstetric and gynecologic indications [12].

In obstetric or gynecologic use, MS can be administrated widely via vaginal as well as oral or sublingual. The pharmacokinetics of MS showed that serum concentrations of vaginally administered MS were higher than those of orally administered MS [13]. However, the efficacy between vaginal route and oral/sublingual route was known to be equivalent and oral/sublingual route is much easier to take than vaginal route. Previous studies reported the effectiveness of sublingual MS [14-16].

In Korea, the usage of MS for obstetric indications has not been approved yet, and there is a paucity of information regarding the efficacy or safety of obstetrical applications of MS. Our institution obtained the approval for the off-label use of MS in obstetric indications by Health Insurance Review and Assessment Service (HIRA) since 2012 and has regularly

submitted the usage performance reports. Therefore, this research has a merit that it is distinguished from other papers in that it is a single institute research on Korean people.

In this study, we tried to determine the effectiveness and safety of medical treatment with off-label usage of sublingual MS in the 1st trimester miscarriage, and find contributing factors associated with the successful medical treatment.

Materials and methods

The study population was consisted of patients who were diagnosed with miscarriage before 14 weeks of gestation in Seoul Metropolitan Government-Seoul National University Boramae Medical Center between April 2013 and June 2016. Those who wanted to avoid surgical intervention and waited until the next day after taking MS for medical treatment were enrolled in this study. The 1st trimester miscarriage was diagnosed by at least 2 different physicians using detailed ultrasound scan. If the patients met one of the following criteria, they were diagnosed with missed abortion: 1) crown-rump length (CRL) of at least 7 mm and no heartbeat; 2) mean gestational sac diameter of at least 25 mm and no embryo; 3) no embryo with heartbeat on a follow-up scan at least 2 weeks after an initial ultrasound scan that showed a gestational sac without a yolk sac; 4) no embryo with heartbeat on a follow-up scan at least 11 days after an initial ultrasound scan that showed a gestational sac with a yolk sac [4]. Once the miscarriage was confirmed, additional sonographic findings were examined such as size or location of uterine leiomyomas if exist, extent of subchorionic hematoma and shape of intra-uterine gestational sac. The corrected gestational age was determined by measurement of the size of gestational sac or CRL at the point of diagnosis of miscarriage by ultrasound. Patients not suitable for medical abortion with MS were excluded: presence of considerable vaginal bleeding, suspected molar or ectopic pregnancy, or contraindication to prostaglandin.

Participants took 600 microgram (mcg) of MS sublingually as initial dose, and repeated the same dose 4–6 hours apart according to the one of the established regimens of MS for the 1st trimester missed abortion [17-21]. At least 12 hours later after the first dose, patients were examined by ultrasound scan to verify whether gestational products were remained in the uterine cavity or not. Successful medical

abortion was defined as spontaneous expulsion of gestational products. If gestational products were not expelled spontaneously, surgical evacuation was performed at least 24 hours later from the initial dose. We defined the successful medical treatment group as patients with spontaneous expulsion of gestational products only by sublingual MS, and the failed medical treatment group as those who remained gestational products despite medications. We evaluated the side effects, such as fever, chilling sense, nausea, vomiting, abdominal pain or diarrhea after administration of MS by using medical records.

The statistical analysis was performed using SPSS version 20.0 for windows (SPSS Inc., Chicago, IL, USA). Comparison of the continuous variables was carried out using the Mann-Whitney *U* test, and proportions were compared using Pearson's χ^2 test. A probability value of <0.05 was considered statistically significant.

This study was approved by the institutional review board of Seoul Metropolitan Government Seoul National University Boramae Medical Center (IRB No. 16-2016-34).

Results

A total of 91 patients was included in this study. Most of them were hospitalized for medical abortion, and the other 3 patients who did not want to be hospitalized took MS at their home. About two-thirds of patients (56/91, 61.5%) had a successful outcome until the next day only after taking sublingual MS. They were classified as the successful medical treatment group, and the other 35 patients as the failed medical treatment group. There were no statistical differences between the two groups in terms of age, body mass index (BMI), parity, history of previous vaginal delivery, original gestational age and corrected gestational age (Table 1). In the successful medical treatment group, the median interval time and range from pill to expulsion of gestational products was 18 hours (4.0–25.0). We tried to find the contributing factors of successful medical abortion with sublingual MS. However, presence or absence of uterine leiomyomas, subchorionic hematoma, or distorted shape of gestational sac on ultrasound scan were not statistically different between the groups. Vaginal spotting before diagnosis of miscarriage had been developed in 25.0% of patients of the

Table 1. Clinical characteristics of study population

Characteristics	Successful medical treatment group (n=56)	Failed medical treatment group (n=35)	P-value
Age (yr)	32 (29–44)	30.5 (27–45)	0.253
BMI	22.7 (18.9–34.7)	23.0 (17.7–32.7)	0.254
Nulliparity	21 (37.5)	17 (48.6)	0.383
Previous vaginal delivery	23 (41.1)	10 (28.6)	0.480
Original gestational age (wk) ^{a)}	9.1 (5.0–13.1)	8.6 (6.6–13.6)	0.618
Corrected gestation age (wk) ^{b)}	6.3 (4.0–12.0)	6.3 (4.0–12.9)	0.745

Values are given as number (%) or median (range).

BMI, body mass index.

^{a)}Known gestational age determined from last menstrual period or confirmed by ultrasound before diagnosis of miscarriage; ^{b)}Gestational age determined by ultrasound at the point of diagnosis as miscarriage.

Table 2. Comparison of associated ultrasound findings and presence of vaginal spotting at diagnosis of miscarriage

Diagnosis	Successful medical treatment group (n=56)	Failed medical treatment group (n=35)	P-value
Ultrasound findings			
Uterine leiomyoma	7 (12.5)	5 (14.3)	0.636
Subchorionic hematoma	5 (8.9)	4 (11.4)	0.917
Distorted shape of gestational sac	4 (7.1)	2 (5.7)	0.789
Vaginal spotting before diagnosis of abortion	14 (25.0)	5 (14.3)	0.221

Values are given as number (%).

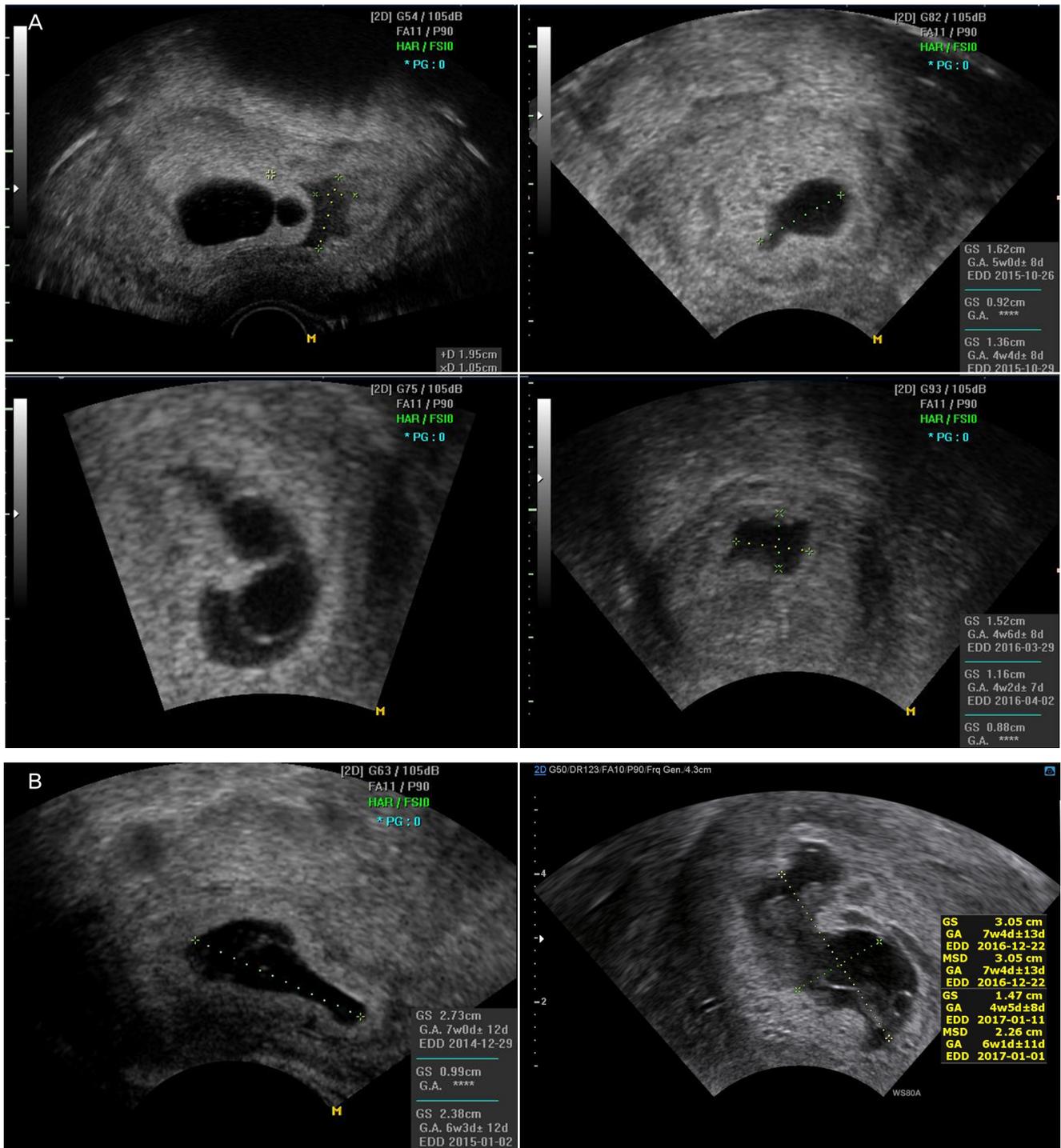


Fig. 1. Six cases of distorted gestational-sac. (A) Cases in group of successful medical abortion: 4 cases. (B) Cases in group of failed medical abortion: 2 cases.

successful medical treatment group, in 14.3% of those of the failed medical treatment group (Table 2). Fig. 1 showed the ultrasound findings of distorted shape of gestational sac in six cases.

The most common side effect was abdominal pain (less than numeric rating scale [NRS] 3 points), and most patients tolerated the symptoms without pain killers. In addition, some patients complained of fever, chilling, loose stool (mild diar-

Table 3. Side effects (multiple answers available)

Side effects	Successful medical treatment group (n=56)	Failed medical treatment group (n=35)
None	6 (10.7)	2 (5.7)
Fever	1 (1.8)	1 (2.9)
Chilling	2 (3.6)	1 (2.9)
Nausea/vomiting	1 (1.8)	0 (0.0)
Abdominal pain (NRS <3)	42 (75.0)	29 (82.9)
Mild diarrhea (loose stool)	1 (1.8)	1 (2.9)

Values are given as number (%).
NRS, numeric rating scale.

reha), and nausea/vomiting (Table 3). However, there was no serious side effect.

Discussion

The principal findings of this study were following: 1) gestational products were spontaneously expelled in about two-thirds of patients with only sublingual MS until the next day; 2) the median interval time from pill to expulsion of gestational products was 18 hours in the successful medical treatment group; 3) there was no serious systemic side effect or massive vaginal bleeding during the medical treatment.

In Korea, MS for obstetric indications has not been approved and used as off-label. Our institution obtained the approval about usage of MS for the 1st trimester medical abortion since 2012, and regularly reported our experiences to the HIRA. As shown in this study, we obtained considerably promising outcome in terms of efficacy and safety despite a small number of cases. Sublingual MS in the 1st trimester miscarriage can be a proper option to the patients who have fear about surgery and anesthesia, and want to avoid any surgical intervention.

Although we conducted surgical evacuation the next day for the remained gestational products in this study, it is also possible to observe more without surgical intervention. If the patients in the failed medical treatment group took additional MS and waited a few more days, the rate of successful medical treatment would have increased. There was a case, not included in this study, whose gestational products were expelled spontaneously after 50 hours later after the adminis-

tration of MS. In according to the previous studies, there were lots of observational data about stepwise administration of MS for 3 to 7 days. As several studies about home administration of oral MS in the 1st trimester miscarriage have shown, if the patients want to wait more with patience, we can take account of her additional MS at home [11,22,23].

A pharmacokinetics-related study addressed that the plasma concentrations of MS was higher in vaginal insertion than in oral administration, but several serious complications were associated with vaginal misoprostol such as premature separation of placenta, postpartum hemorrhage, uterine rupture and amniotic fluid embolism in patients with fetal demise [24,25]. Tang et al. [16] reported that the efficacy of sublingual MS was similar with vaginal MS in patients with miscarriage, but the mean interval time between administration of MS and passage of product of conceptions might be shorter in patients with sublingual MS than those with vaginal MS, 9.5 hours and 13.5 hours, respectively, although the difference was not statistically significant.

The most common complications after administration of sublingual MS in this study was abdominal pain below NRS 3 point, and in a few cases, fever, chilling, loose stool (mild diarrhea), or nausea/vomiting was developed. There was no severe or serious side effect.

There is no exact definition of the normal shape for gestational sac, but on obstetric ultrasound, the gestational sac looks like a dark ("anechoic") space ("cyst") surrounded by a thick white ("hyperechoic") rim. Normally, it is spherical in shape, and usually located in the upper part of the fundus of the uterus [26]. As shown in Fig. 1, six cases of 91 patients appeared distorted gestational sac on ultrasound scan. Distorted gestational sac was not a statistically associated with the successful medical treatment in this study with small sample size.

In spite of recent advances in surgical techniques and perioperative care, surgical curettage of the gravid uterus is a risk factor for intrauterine adhesions and abnormally invasive placenta in subsequent pregnancy [27,28]. Spontaneous expulsion of gestational product induced by MS dose not hurt uterus.

According to the 2006 WHO Frequently asked clinical questions about medical abortion, several factors should be taken into account when counseling a woman about her choice between medical and surgical abortion [29]. Besides of patients who want to avoid surgical intervention and anesthesia, there

are several favorable conditions for medical abortion as follows; 1) very early gestation; up to 49 days of gestation, medical abortion is considered to be more effective than surgical abortion; 2) severe obesity (BMI greater than 30); 3) uterine malformations or a fibroid uterus, or previous cervical surgery. Maternal severe obesity or uterine malformation make surgical intervention difficult [29]. Although not included in this study, there was a case transferred from local clinic to our hospital because of failed surgical treatment of miscarriage. She had a bicornuate uterus, and gestational products were located in the right uterus. We tried to evacuate the gestational products surgically, but eventually failed to access to the right uterus with gestational products. She took 600 mcg of MS and repeated the same dose 4 hours later. After 14 hours later since the initial pill, the gestational products came down to the external os of cervix on examination, so we easily removed the gestational products.

There are several strengths and limits of this study. This is the first study in Korea, based on data of sublingual MS in obstetric applications under supervision of the HIRA. Despite, the limitations of our study are attributable to the inherent weakness of a retrospective study and small sample size. If further prospective studies with a large population identify some contributing factors associated with successful medical treatment, it will be helpful in the counseling of patients.

In conclusion, medical treatment with sublingual MS can be a proper option for the 1st trimester miscarriage without any serious complications, especially for the patients who want to avoid surgical procedure. We can reduce the unnecessary sedation or surgical intervention in the patients with the 1st trimester miscarriage.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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