

COMPARISON OF INTRACERVICAL LAMINARIA PLUS VAGINAL MISOPROSTOL AND VAGINAL MISOPROSTOL ONLY WITH VARIABLE DOSAGES FOR MEDICAL ABORTION WITHIN 12 HOURS

Jae Eun Shin, MD, Ji Young Kwon, MD, Young Lee, MD, Jong Chul Shin, MD, In Yang Park, MD

Department of Obstetrics and Gynecology, The Catholic University of Korea School of Medicine, Seoul, Korea

Objective

To compare the effectiveness of intracervical laminaria plus vaginal misoprostol and vaginal misoprostol only with variable dosages by analyzing the rate of spontaneous gestational sac expulsion for medical abortion within 12 hours.

Methods

This study was performed in 94 patients for missed abortion at Department of Obstetrics and Gynecology, St. Paul's Hospital, the Catholic University of Korea for 5 years (2004-2008). Forty seven patients were managed with laminaria insertion and intravaginal misoprostol 200 µg, 400 µg, or 800 µg at admission or outpatient clinic. The others were treated with only misoprostol at the same dose. We analyzed the rate of spontaneous expulsion of gestational sac within 12 hours.

Results

In non-laminaria group, spontaneous expulsion rate increased according to the doses of misoprostol (4.2%, 37.5%, and 33.3%, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.028$). Between groups with the same misoprostol doses, no difference was observed in the spontaneous expulsion of the fetal sac within 12 hours according to the use of laminaria. On multivariate logistic regression analysis, factors that were associated significantly and independently with spontaneous expulsion of conceptus were misoprostol ≥ 400 µg and gestational age.

Conclusion

Treatment of missed abortion with 400 or 800 µg misoprostol vaginally is safe and acceptable method, and reduced the number of surgical interventions.

Keywords: Misoprostol; Laminaria; Missed abortion; Pregnancy

Curettage has been the method of choice for treatment of spontaneous abortion from the past. However, such a surgical treatment method can induce abortion-related complications such as bleeding, infection, and uterine damage and perforation, and increase maternal morbidity, and even in some cases it has been reported to be related to maternal death [1,2]. Medical therapy is applied in order to solve these shortcomings of the surgical method, and among drugs used in medical treatment, prostaglandin is effective for uterine contraction and cervical ripening, and especially prostaglandin E_2 (PGE₂) shows an outstanding effect on medical abor-

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Corresponding author: In Yang Park, MD

Department of Obstetrics and Gynecology, Seoul St. Mary's Hospital, The Catholic University of Korea School of Medicine, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea

Tel: +82-2-2258-6173 Fax: +82-2-595-1549

E-mail: ooooobbbb@catholic.ac.kr

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tion [3]. However, PGE₂ is expensive, and is not easy to be stored because of its chemical instability at room temperature. Moreover, it is accompanied with many gastrointestinal and cardiovascular side effects [4,5].

Recently emerging misoprostol, which is a synthetic derivative of PGE₁, has been used as a drug for duodenal ulcer, but is extended to be used in obstetric field, such as induction of labor and abortion, because it induces cervical dilatation and uterine contraction [6,7]. In addition, it is inexpensive and storable at room temperature, and causes fewer side effects [6,7]. Much research has been carried out to define the most effective and best tolerated dosage and route of administration, but previous studies have reported its success rate mostly within 24 hours [8,9].

In this study, we compared the effectiveness of intracervical laminaria plus vaginal misoprostol and vaginal misoprostol only with variable dosages by analyzing the rate of spontaneous gestational sac expulsion for medical abortion within 12 hours.

Materials and Methods

This study was conducted through analyzing medical records

retrospectively, and the subjects were patients that visited the hospital for missed abortion in the 1st trimester and terminated pregnancy with medical management during five years (January 1, 2004–December 31, 2008). During the period, a total of 103 patients visited for missed abortion as principal diagnosis, and were randomly administered different doses of misoprostol and/or laminaria. Exclusion criteria were inevitable abortion or incomplete abortion, administration of 600 µg misoprostol vaginally, and oral administration of misoprostol. A total of 94 patients were included in the final analysis. They were divided into the group with laminaria inserted and that without, and each group was subdivided into three groups according to misoprostol dose (200 µg, 400 µg, and 800 µg).

In our hospital, misoprostol and/or laminaria were inserted vaginally in the evening of admission day, and after 12 hours on the next morning the expulsion of the fetal sac was confirmed by ultrasound. If the gestational sac was expelled spontaneously, the patient was discharged, and if not, curettage was performed. After that, patients were followed up after 1 week. We analyzed the fetal sac and embryo size to the accurate gestational age, and accompanying symptoms such as bleeding and low abdominal pain. In order to compare the effectiveness between the treatment

Table 1. Maternal characteristics

Characteristics		Non-laminaria group	Laminaria group	P-value
Misoprostol 200 µg	Patients (n)	24	27	
	Age (yr)	32.3 ± 5.1	30.1 ± 4.4	0.110
	Gestational age (day)	61.8 ± 15.8	65.4 ± 17.4	0.443
	Gravida (n)	1.7 ± 1.3	1.3 ± 1.6	0.376
	Parity (n)	0.5 ± 0.7	0.6 ± 0.7	0.798
	Cesarean delivery history (n)	4	6	0.618
Misoprostol 400 µg	Patients (n)	8	10	
	Age (yr)	28.4 ± 4.2	32.6 ± 6.7	0.138
	Gestational age (day) ^a	52.4 ± 12.8	93.7 ± 26.7	0.001
	Gravida (n)	1.8 ± 1.4	2.2 ± 1.8	0.571
	Parity (n)	0.6 ± 0.7	0.6 ± 0.8	0.948
	Cesarean delivery history (n)	1	0	0.250
Misoprostol 800 µg	Patients (n)	15	10	
	Age (yr) ^a	34.7 ± 4.9	29.2 ± 3.3	0.006
	Gestational age (day) ^a	66.8 ± 15.8	91.3 ± 27.4	0.040
	Gravida (n)	2.0 ± 2.1	0.7 ± 0.8	0.162
	Parity (n)	0.6 ± 0.9	0.3 ± 0.5	0.637
	Cesarean delivery history (n)	1	2	0.315

^aP-value < 0.05.

methods, we reviewed age, gestational age, and prior pregnancy history, such as gravida, parity, and cesarean delivery history. Statistical analysis was used by XLSTAT ver. 2011.2.06 (Addinsoft, New York, NY, USA), and comparative analysis was performed by chi-square test for differences in qualitative variables and Student *t*-test for differences in continuous variables. A multivariate logistic regression model was constructed to identify independent risk factors associated with spontaneous expulsion rate and to control for confounders. Odds ratios and their 95% confidence interval were computed. Statistical significance was accepted if *P*-value<0.05.

Results

Of the 94 pregnant women who visited for therapeutic pregnancy termination due to missed abortion, 47 had both the insertion of laminaria and the vaginal insertion of misoprostol, and the dose of misoprostol was 200 µg in 27 of them, 400 µg in 10, and 800 µg in 10. In addition, 47 patients had only the vaginal insertion of misoprostol, and the dose of misoprostol was 200 µg in 24 of them, 400 µg in 8, and 800 µg in 15.

Maternal characteristic were analyzed in Table 1. In comparison with groups of different dosages of misoprostol, patients were not

statistically different from each other in respect to age (31 years, 31 years, and 32 years, in 200 µg, 400 µg, and 800 µg, respectively, *P*=0.245), gravida (1, 2, and 1, in 200 µg, 400 µg, and 800 µg, respectively, *P*=0.585), parity (0.6, 0.6, and 0.5, in 200 µg, 400 µg, and 800 µg, respectively, *P*=0.851) and cesarean delivery history (10, 1, and 3, in 200 µg, 400 µg, and 800 µg, respectively, *P*=0.317). In gestational age, patients with 200 µg of misoprostol were lower than women with 400 µg and 800 µg (64 days, 75 days, and 77 days, in 200 µg, 400 µg, and 800 µg, respectively, *P*=0.027). In addition, these patients were divided into two groups according to the use of laminaria, and each group was subdivided into the 200 µg group, the 400 µg group, and the 800 µg group according to misoprostol dose. Table 1 shows the maternal age, gestational age, and prior pregnancy history, and statistically significant differences were observed in gestational age between the 400 µg groups, and age and gestational age between the 800 µg groups. No other statistical difference was observed.

We compared symptoms on admission such as vaginal bleeding and low abdominal pain among the groups, and found no significant difference (Table 2). In addition, ultrasonographic findings were compared in terms of gestational sac size, embryo size, and the presence of hematoma, and no difference was observed among the groups. In comparison with groups of different dos-

Table 2. Maternal symptoms and sonographic findings

Characteristics	Non-laminaria group	Laminaria group	<i>P</i> -value
Misoprostol 200 µg			
Patients (n)	24	27	
Vaginal bleeding (n)	15	11	0.121
Abdominal pain (n)	4	5	0.863
Gestational sac size (mm)	32.0 ± 18.4	28.4 ± 17.8	0.360
Embryo size (mm)	13.6 ± 11.8	11.0 ± 12.1	0.345
Subchorionic hematoma (n)	6	2	0.085
Misoprostol 400 µg			
Patients (n)	8	10	
Vaginal bleeding (n)	3	5	0.596
Abdominal pain (n)	2	1	0.396
Gestational sac size (mm)	30.5 ± 14.8	39.0 ± 21.6	0.583
Embryo size (mm)	17.0 ± 7.2	24.4 ± 26.2	0.643
Subchorionic hematoma (n)	1	0	0.250
Misoprostol 800 µg			
Patients (n)	15	10	
Vaginal bleeding (n)	8	3	0.250
Abdominal pain (n)	3	3	0.566
Gestational sac size (mm)	29.3 ± 20.4	25.0 ± 10.2	0.752
Embryo size (mm)	12.8 ± 9.6	16.7 ± 14.5	0.759
Subchorionic hematoma (n)	2	2	0.656

Table 3. Spontaneous expulsion rate of conceptus

Characteristics		Non-laminaria group	Laminaria group	P-value
Misoprostol 200 µg	Patients (n)	24	27	
	Spontaneous Expulsion cases (n)	1	2	0.623
	Spontaneous Expulsion rate (%)	4.2	7.4	
Misoprostol 400 µg	Patients (n)	8	10	
	Spontaneous Expulsion cases (n)	3	2	0.410
	Spontaneous Expulsion rate (%)	37.5	20	
Misoprostol 800 µg	Patients (n)	15	10	
	Spontaneous Expulsion cases (n)	5	3	0.861
	Spontaneous Expulsion rate (%)	33.3	30.0	

Table 4. Factors associated with increased risk of spontaneous expulsion of conceptus

Characteristics	Unadjusted OR			Adjusted OR ^{as}		
	OR	95% CI	P-value	OR	95% CI	P-value
Misoprostol ≥ 400 µg ^b	6.93	1.64-33.68	0.004	5.028	1.127-22.442	0.034
Gestational age ^b	1.036	1.011-1.061	0.004	1.050	1.013-1.089	0.008
Laminaria	0.736	0.250-2.182	0.584	0.242	0.044-1.337	0.104
Previous abortion	1.847	0.611-5.578	0.277	1.109	0.272-4.521	1.109
Previous vaginal delivery	1.157	0.360-3.715	0.806	1.118	0.247-5.074	0.885

Values are expressed as odds ratio (OR) (95% confidence interval [CI]).

Results of multivariate logistic regression.

^aAdjusted by age, vaginal bleeding, abdominal pain, subchorionic hematoma.

^bP-value<0.05.

ages of misoprostol, patients were not statistically different from each other in respect to vaginal bleeding (26, 8, and 11, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.805$), abdominal pain (9, 3, and 6, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.769$) gestational sac size (29 mm, 34 mm and 29 mm, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.959$) embryo size (12 mm, 21 mm and 14 mm, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.103$), and subchorionic hematoma (8, 1, and 4, in 200 µg, 400 µg and 800 µg, respectively, $P=0.527$).

Spontaneous expulsion rate of conceptus within 12 hours was analyzed in Table 3. In non-laminaria group, spontaneous expulsion rates increased according to the doses of misoprostol (4.2%, 37.5%, and 33.3%, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.028$). In laminaria group, spontaneous expulsion rates were higher in the 400 µg, and 800 µg subgroups than 200 µg subgroup, but not significant statistically (7.4%, 20%, and 30%, in 200 µg, 400 µg, and 800 µg, respectively, $P=0.077$). Between groups with the same misoprostol dose, no difference was observed in the spontaneous expulsion of the fetal sac within 12 hours according to the use of laminaria.

On multivariate logistic regression analysis, factors that were associated significantly and independently with spontaneous expulsion of conceptus were misoprostol ≥ 400 µg and gestational age (Table 4). Laminaria insertion, previous abortion history and previous vaginal delivery were unrelated to increased risk of spontaneous expulsion. No one visited emergency room or needed hospitalization for abdominal pain, vaginal bleeding or infection within 1 week of follow-up. No one required transfusion or additional curettage.

Discussion

For medical abortion, it is known that combined regimen of mifepristone (antiprogesterone) and prostaglandin is more effective than prostaglandin alone, but misoprostol alone is widely used in some parts of the world, including Korea, where mifepristone is not available [10]. The reported complete abortion rate for misoprostol alone varies between 33% to 60% for single dose and 93% for repeat doses [10]. The success rates of medically-treated first trimester miscarriages varied according to dosages and route

of misoprostol, the ultrasonographic definitions of pregnancy failure, time of assessment, and the criteria for success [11]. Of the different routes of misoprostol administration, vaginal route appears to be superior to oral, sublingual and buccal administration in terms of efficacy, and has fewer side effects when compared to other routes [11]. A regimen of 800 µg of misoprostol administered vaginally every 24 hours for up to three doses achieved complete abortion rates in 88% to 91% of women who were <8 weeks pregnant. This regimen takes several days [12,13]. Another regimen using 800 µg of misoprostol (administered vaginally) as an initial dose followed by 400 µg of misoprostol (administered orally) every 3 hours for three to four doses achieved complete abortion rates in 70%-85% of women [14,15].

In case pregnancy termination is performed for missed abortion in the 1st trimester, the first consideration is whether to use drug treatment or surgical treatment, and also it should be considered how to reduce the patient's anxiety and guilty feeling. In order to relieve them, we need to minimize the number of hospital visits or hospital stay and this consideration is also meaningful in terms of expenses [16,17]. According to previous reports, when misoprostol was administered the probability of the successful spontaneous expulsion of the fetal sac within 24 hours was around 80%, but it is practically difficult to wait for 24 hours after the administration of the drug [18]. One of the reasons is that outpatient follow-up after the vaginal insertion of misoprostol may result in abdominal pain or vaginal bleeding at an unpredictable time and this may cause many troubles to the patient and guardian including admission to the emergency room. For these reason, the authors compared patients who had both the insertion of laminaria and the vaginal insertion of misoprostol with those who had only the vaginal insertion of misoprostol in order to see the probability of the spontaneous expulsion of the fetal sac within 12 hours and which treatment is more successful with less pain and discomfort. In our study, all women with a spontaneous expulsion, which was no gestational sac in endometrium confirmed by ultrasound, did not need to undergo additional surgical management. It is known that if no gestational sac is present, in the absence of heavy bleeding, intervention in most women is unnecessary [19]. This is true even when, as is common, the uterus contains sonographically evident debris [19].

Misoprostol is known as a safe agent for early pregnancy failure, but precautions should be taken into consideration in some complications and side-effects. Diarrhea is the major adverse reaction, but it is usually mild and self-limiting [20]. Fever and chills have also been reported, but are more associated with higher doses in

the third trimester or immediate postpartum period [20]. In addition, medical methods are associated with a longer duration of bleeding than surgical methods [10]. Another concern is the risk of uterine rupture, especially in women with a previous uterine scar. Reports of uterine rupture are rare in first trimester medical abortion, but the risk seems to increase with gestation [20,21]. Exposure to misoprostol in early pregnancy has been associated with multiple congenital defects, therefore, counsel the women on the risk of fetal abnormality if the pregnancy is continued after exposure to misoprostol [20,22].

According to the results of this analysis, the use of laminaria did not have an effect on the spontaneous expulsion of the fetal sac. In addition, among those who had the vaginal insertion of misoprostol, the success rate was highest when the misoprostol dose was 400 µg and 800 µg. In conclusion, the vaginal insertion of misoprostol was safe and acceptable method for therapeutic pregnancy termination for missed abortion in the 1st trimester, and reduced the number of surgical intervention.

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12시간 이내의 치료적 유산을 위한 자궁경부 내 라미나리아 및 미소프로스톨 병합투여와 미소프로스톨 단독요법의 비교

가톨릭대학교 의과대학 산부인과학교실

신재은, 권지영, 이 영, 신종철, 박인양

목적

임신 첫 삼분기 계류유산 치료에 있어 12시간 이내에 자연적으로 태낭이 배출되는 빈도를 분석함으로써 라미나리아와 미소프로스톨을 사용하는 경우와 미소프로스톨만을 사용하는 경우의 효과를 비교하고자 하였다.

연구방법

최근 5년간 계류유산으로 진단받고 치료적 임신 중절을 시행받은 94명을 분석 대상으로 하여 후향적으로 분석하였으며, 이 중 47명은 라미나리아를 사용하였으며 이들은 미소프로스톨 사용량에 따라 200 µg, 400 µg, 800 µg 군으로 각기 나누었으며 라미나리아를 사용하지 않은 군도 같이 분류하였다. 각 군에서 치료 시행 후 12시간 이내에 태낭이 자연 배출되는 경우를 통계 분석하였다.

결과

라미나리아를 사용하지 않은 그룹에서 자연배출 빈도는 미소프로스톨의 용량에 따라 증가하였다(각각 200 µg, 400 µg과 800 µg에서 4.2%, 37.5%와 33.3%, $P=0.028$). 같은 미소프로스톨 용량의 그룹 간 비교에서, 라미나리아 사용 여부에 따른 12시간 이내 자연배출의 빈도는 차이가 없었다. 다변량 로지스틱 회귀 분석에 따르면, 유산물의 자연 배출 빈도는 400 µg 용량 이상의 미소프로스톨과 임신 재태 연령과 의미있고 독립적으로 관련이 있었다.

결론

계류유산 치료에 있어 질내로 삽입하는 미소프로스톨은 효과적이고 안정적인 약제로 사용할 수 있으며, 12시간 이내 자연적으로 태낭이 배출되는 확률은 400 µg, 800 µg을 사용하는 경우 가장 높았다.

중심단어: 미소프로스톨, 라미나리아, 계류유산, 임신