EVALUATION OF THE EFFECTIVENESS OF ORAL AND VAGINAL MISOPROSTOL FOR INTRAUTERINE FETAL DEATH AND FETAL ANOMALY IN SECOND TRIMESTER PREGNANCY TERMINATION: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background: *which method of the expulsion of intrauterine fetal death and fetal anomaly in second trimester is effective, safe, and suitable for pregnant women.* ***Objectives:*** *to evaluate the effectiveness of oral misoprostol and vaginal misoprostol for intrauterine fetal death and fetal anomaly in second trimester pregnancy termination.* ***Materials and Methods:*** *a clinical trial in 108 women experiencing intrauterine fetal death and fetal anomaly during the second trimester in the obstetric department, Can Tho central general hospital in 2014. Excluded criteria: multiple pregnancies, uterus cesarean section scar, and misoprostol contraindication. Intervention: randomized division into two groups: group 1: misoprostol oral, group 2: vaginal misoprostol; dosage as recommended by FIGO. Success was defined as a complete and natural fetal and placenta expulsion without dilation and curettage or other treatment; and healthy hospital discharge.* ***Results****: the success rate of group 1 was 75.9%; group 2 was 83.3%. The success rates for fetal conditions of intrauterine fetal death were 74.6%, and the fetal anomaly was 86.7%. In group 1, the success rate in intrauterine fetal death was 63%, fetal anomaly was 88.9%. In group 2, the success rate in intrauterine fetal death was 81.3% and fetal anomaly was 86.4%. The rate of expulsion in the first 24 hours was 78.1% in group 1; 88.9% in group 2, which was not different statistically. Some side effects encountered in the study such as headache, nausea, diarrhea, fever/chills, rash were mainly seen in the oral misoprostol group; all side effects and complications were mild and transient. Related factors to complete expulsion in both groups were gestational age, parity, and fetal conditions.* ***Conclusion:*** *vaginal misoprostol has the same effectiveness and fewer complications than oral misoprostol****.***

Keywords: *fetal anomaly; intrauterine fetal death; pregnancy termination; oral misoprostol; vaginal misoprostol.*

I. INTRODUCTION

Termination of pregnancy for severe fetal anomaly and intrauterine deaths must be done as soon as possible for pregnant women to reduce the rate of live birth defects or complications caused by intrauterine fetal death. Besides, decrease in physical and mental injuries for mothers as well as burdens on families and society. The issue is in choosing which method to use to terminate a pregnancy while ensuring the safety of pregnant women. Therefore, the study increasingly requires finding the optimal medical abortion methods, which are highly effective, safe, and more acceptable for women. In the last decade, there has been a lot of progress in induced abortion techniques; moreover, the use of medication to terminate a pregnancy in the second trimester has grown significantly because of its high effectiveness, safety, and popular approval. Misoprostol is a product of synthetic Prostaglandin of the E1 group, which causes the cervix to ripen, soften, and dilate [5].

Consequently, obstetricians have used this pharmacological effect to induce abortion in the second trimester of pregnancy. This method has been applied worldwide since the 1980s and has been studied in Vietnam since 1992. However, there is still a lot of controversy about the dosage, route of administration, as well as the results of MSP and the adverse effects in the abortion of large fetuses [6], [7].

II. MATERIALS AND METHODS

2.1 Research design:

A randomized controlled clinical trial study in 108 pregnant women with singleton gestation from 14 to 28 weeks, having no uterine scar, no contraindication of misoprostol, and having indications for the necessity of induced terminations due to intrauterine fetal deaths or severe fetal malformations in the Obstetrics department of Can Tho Central General Hospital in 2014, are randomly divided into 2 clinical experimental groups with Misoprostol. However, cases of pregnant women, who had signs of threatened miscarriage or inevitable miscarriage as well as women who had used any previous abortion methods, would be excluded from this study. The first group receiving oral misoprostol included selected pregnant women with odd numbers from 1 to 53. The second group using vaginal misoprostol included pregnant women with even numbers from 2 to 54.

2.2 Implementation steps:

All pregnant women in the two study groups were given the same dose of misoprostol, depending on the gestational age according to FIGO 2009 (International Federation of Gynecology and Obstetrics) [3]: Gestational age < 18 weeks: misoprostol 200µg q6hr; gestational age 18 - 26 weeks: misoprostol 100µg q6hr (no more than 3 times/day); gestational age ≥ 27 weeks: misoprostol 25 - 50µg q4hr.

If it were unsuccessful, misoprostol (MSP) could be taken at the same dose in the following days. Total days of misoprostol administration were no more than 3 consecutive days (one course of medication). If it failed after a course of medication, it was reused in the second period after one week. After the first dose of misoprostol, women were monitored every 4-6 hours until the fetus came out. Criteria for evaluating the success rate of the study were naturally expelling fetuses, natural placenta expulsion in each period of medication administration with unlimited time and without any medical device intervention into the uterus chamber or right switch to another treatment, as well as any complication such as: abnormal uterine action, hemorrhage, retained placenta, infection, cervical tear, uterine rupture, etc. Moreover, it is not necessary to stop the treatment regimen because of the adverse effects of MSP, and postpartum women were evaluated as completely healthy before leaving the hospital.

- For cases of non-expulsion, they will be appropriately individually managed to achieve the health expectations of pregnant women.
- Postpartum period: monitor overall conditions, pulse, blood pressure, uterine contraction, and vaginal bleeding every 30 minutes for the first 2 hours, then every 6 hours.

During the pregnancy termination period, we compared the effectiveness of two ways of Misoprostol administration, which were oral and vaginal routes, based on the evaluation of the duration of induced labor, the time of the expulsion of a dead fetus out of the uterus, as well as

adverse effects of each method. At the same time, we also searched for some factors related to the effectiveness of oral and vaginal MSP usage on fetal status.

Statistical analysis: Enter and analyze data using SPSS 18.0 software.

Ethics approval: Misoprostol dosage in this research was use as guideline of Vietnam ministry of health.

III. RESULTS

Table 1. Study population characteristics

Characteristics		Group 1		Group 2		Total	
		n=45	%	n=45	%	n	%
Job	Farmers	13	24.1	16	29.6	29	26.9
	Saleswomen	7	13.0	4	7.4	11	10.2
	Officers	2	3.7	3	5.6	5	4.6
	Housework	23	42.5	26	48.1	49	45.3
	Workers	4	7.4	2	3.7	6	5.6
	Others	5	9.3	3	5.6	8	7.4
Parity	Para 0	28	51.9	27	50.0	55	50.9
	Para 1 – 2	24	44.4	26	48.1	50	46.3
	Para ≥ 3	2	3.7	1	1.9	3	2.8
Maternal age (years)		29.81 ± 6.66		28.37 ± 5.95		29.09 ± 6.33	
Gestational age (weeks)		18.78 ± 4.68		18.06 ± 4.35		18.42 ± 4.51	

Data are presented as mean ± SD

The main occupation in the research was housework 45,3%; 50.9% of pregnant women did not have a history of childbirth, 2.8% of pregnant women had histories of more than 3 childbirths. The average age of pregnant women in the study was 29.09 ± 6.33 years. Pregnant women had a mean gestational age of 18.42 ± 4.51 weeks.

Table 2. The success rate of misoprostol

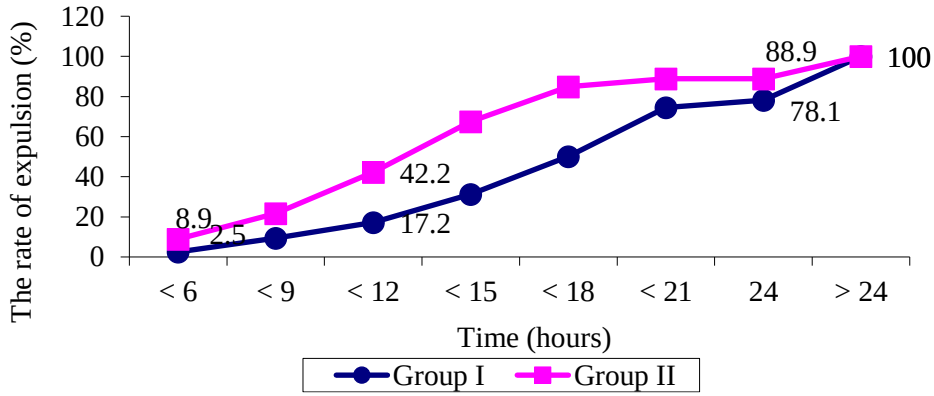
Characteristics		Success		Failure		Total	
		n=86	%	n=22	%	n=108	%
MSP group used	Group 1	41	75.9	13	24.1	54	100
	Group 2	45	83.3	9	16.7	54	100
	General group	86	79.6	22	20.4	108	100
	p, OR (95%CI)	0.34; 0.631 (0.24 – 1.63)					
Fetal conditions	Intrauterine fetal death	43	72.9	16	27.1	59	100
	Fetal anomaly	43	87.8	6	12.2	49	100
	p; OR (95%CI)	0.06; 0.38 (0.13 – 1.05)					

The overall success percentage of MSP termination of pregnancy was 79.6% (75.9% in group 1; 83.3% in group 2). However, this difference was not statistically significant with $p > 0.05$. The success rate of misoprostol depending on fetal status was not significantly statistically different with $p > 0.05$.

Table 3. Success rate by fetal conditions in the two groups

Fetal conditions	Group 1 (Oral misoprostol)				Group 2 (Vaginal misoprostol)			
	Success		Failure		Success		Failure	
	n	%	n	%	n	%	n	%
Intrauterine fetal death	17	63.0	10	37.0	26	81.3	6	18.8
Fetal anomaly	24	88.9	3	11.1	19	86.4	3	13.6
Both	41	75.9	13	24.1	45	83.3	9	16.7
p, OR (95%CI)	0.02; 0.21 (0.05 – 0.89)				0.62; 0.68 (0.15 – 3.09)			

The group 2 had a higher success rate in the group of fetal deformities compared to the stillbirth group (86.4% versus 81.3%), but there was no statistically significant difference with $p > 0.05$. Meanwhile, the success rate was noticeably higher in deformed fetal cases compared to stillbirth in group 1 (88.9% versus 63%), the difference was statistically significant with $p < 0.05$; OR=0,21 (95%CI: 0,05 – 0,89).



p = 0.007

Figure 1: Distribution of expulsion rate between 2 groups by time

Average time of expulsion of the fetus: Group 1: 20.3 ± 9.51 hours; group 2: 16.81 ± 8.02 hours; p = 0.04

The timing of expulsion in group 2 (16.81 ± 8.02 hours) was shorter than in group 1 (20.3 ± 9.51 hours); in the first 24 hours: the rate of expulsion is 88.9% in group 2 and 78.1% in group 1. Although the efficacy of the two study groups was not statistically significant, the timing of the expulsion of the misoprostol vaginal group was significantly statistically shorter than the oral misoprostol group with $p < 0.01$.

Table 4: Factors associated with misoprostol's success rate

Charateristics	Group 1			Group 2			p	OR (95%CI)
	n_0=54	n= 41	%	n_0= 54	n= 45	%		
Age group								
< 35	40	31	77.5	46	37	80.4	0,65	1.4(0.3- 5,4)
≥ 35	14	10	71.4	8	8	100	0.12	0.8 (0.7-0.9)
Gestational age								
14 - < 18	26	19	73.1	31	23	74.2	0.64	0.7(0.2- 2.6)
18 - 28	28	22	78.6	23	22	95.6	0.04	0.13(0.01-1.1)
Parity								
ulliparous	28	25	89.2	27	25	92.6	0.02	5.2(1.2- 21.8)

Charateristics	Group 1			Group 2			p	OR (95%CI)
	n_0=54	n= 41	%	n_0= 54	n= 45	%		
Parous	26	16	61.5	27	20	74.1	0.07	4.4(0.8-23.4)
Fetal conditions								
Intrauterine fetal death	27	17	63.0	32	26	81.3	0.03	0.2(0.05-0.89)
Fetus anomaly	27	24	88.9	22	19	86.4	0.62	0.68(0.15-3.09)

n_0: sample size of each group; n: number of successful cases in each group

In the age group of ≥ 35 years, the success rate was significantly higher in group 2 than in group 1 (100% compared to 71.4%), but the difference was not statistically significant. Similarly, gestational age is not associated with the success rate of the two methods of MSP use with p>0.05. With a history of previously not suffering childbirth, pregnant women in group 2 had a higher success rate than group 1 (92.6% compared to 89.2%) and were determined to be related to the route of MSP use with p < 0.05; 95%CI: 1.2- 21.8. For cases of fetal death, termination of pregnancy with group 2 was more effective than with oral misoprostol with p < 0.05; 95%CI: 0.05- 0.89.

IV. DISCUSSION

The overall success rate of the method of pregnancy termination with misoprostol was 79.6%, in which the oral misoprostol group had a success rate of 75.9%; whereas the vaginal misoprostol group was 83.3%; but through the evaluation, the effect of fetal expulsion between the two groups did not differ significantly with p> 0.05; OR= 0.631 (95%CI: 0.24 – 1.63). Mostafa Gamal Abdelhaleem compared the effectiveness of oral and vaginal misoprostol, the results showed that there was no difference in the efficacy of expulsion between the two groups [11]. Similarly, in a meta-analysis of 18 studies in which 1802 women participated, the conclusion: the efficacy of oral misoprostol is lower than vaginal administration, maybe due to the first effect of the liver which significantly reduces the bioavailability of the drug. But through statistical analysis, the effectiveness of oral misoprostol was equivalent to the vaginal one [7].

Vaginal misoprostol placement also produced a success rate of 89- 95% [1], [13]. The success rate of vaginal misoprostol was not significantly different statistically from the oral misoprostol group [2]. Alka A. Mukherjee concluded that the rate of expulsion of the fetus when using misoprostol vaginally was 94.2%, under the cheek was 95%. The difference was not statistically significant, p = 0.78 [1]. Since evaluating the efficacy of misoprostol for expelling the fetus in two ways of administering the drug (orally and vaginally) to the condition of the fetus (missed miscarriage and fetal anomalies), we concluded that the efficacies were equivalent for both conditions, whether the fetus died or was alive but had structural abnormalities. However, we did not dare to conclude the misoprostol effect on pregnant living healthily. With the pregnant women group using vaginal misoprostol, the overall rate was the same success in fetal anomalies and missed miscarriage (86.4% versus 81.3%). There is no evidence for a need to reduce the dose of misoprostol to expel stillbirth [10]. Meanwhile, in the pregnant group receiving oral misoprostol, the success rate was significantly higher in the fetuses with deformity

compared to the stillbirths (88.9% versus 63%). This difference was statistically significant with $p < 0.05$; OR=0.21 (95%CI: 0.05 – 0.89). The above results, it showed a high success rate of using misoprostol to cause pregnancy termination. It was a non-invasive, low-cost and beneficial method that saved pregnant women from mental and physical trauma as well as social-psychological consequences; therefore, it could be considered as a first-line method for the expulsion of stillbirths and fetal malformations during the second trimester of pregnancy.

Though the efficacy of the two study groups was not statistically significant, the expulsion of fetus by vaginal misoprostol group had a significantly higher rate than that of oral misoprostol with $p<0.01$ as well as the mean expulsion time of using misoprostol vaginally was significantly shorter than that of the group taking misoprostol orally (16.81 ± 8.02 hours versus 20.3 ± 9.51 hours). According to Suyash, the average expulsion period of group using vaginal misoprostol was 18.57 hours and 21.66 hours for the oral misoprostol group [12]. Meanwhile, Alka A. Mukherjee reported that the average expulsion time of sublingual misoprostol group (10.28 ± 3.1 hours) was shorter than the oral group (14.68 ± 4.2 hours) but no significant difference was found in the success rate among the two comparison groups [1].

In group MSP vaginal, the mean expulsion time was 1.07 ± 1.29 days compared to 0.82 ± 0.66 days in group sublingual MSP [8]. The above results show a high success rate when taking misoprostol to expulse the fetus, and this is a non-invasive, low-cost and beneficial method for pregnant women to avoid physical and mental trauma. In terms of psychology and society, it should be considered as a first-line method of the expulsion of a fetus in the second trimester of pregnancy.

A high success rate was achieved from 18 to 28 weeks of pregnancy in both groups using oral misoprostol (78.6%) and vaginal misoprostol (95.6%). This demonstrated that misoprostol's response was higher as the gestational age was greater, so it should be cautious in terms of dosage when using misoprostol to induce labor and the complications have commonly happened at older gestational age groups. Ines Pereira reported the mean gestational age in the study was 18.26 ± 3.2 weeks, in which the successful group's average gestational age was (18.3 ± 0.19 weeks) higher than the group failing with misoprostol (17.4 ± 0.53 weeks) [9]. In both research groups, the success rate of primigravida was higher than that of multigravida. Fatemeh reported that the rate of expelling in nulliparous was higher than that of parous, but the success rate of misoprostol uses in the nulliparous was not different from that of the parous [4]. The success rate in the group of fetal anomalies was higher than that of the intrauterine fetal death in both study groups because the risk of retained placental tissues of intrauterine fetal death was often higher than that of the fetus is still alive, therefore the failure rate would be increasing; terminating intrauterine fetal death with vaginal misoprostol was more effective than taking oral misoprostol with $p <0.05$; OR = 0.2 (95% CI: 0.05- 0.89). Ines Pereira recorded a high success rate in 59.5% of fetal anomalies compared to 16.5% of intrauterine fetal death and the fetal condition affected the efficacy of misoprostol usage in the termination of pregnancy [9].

V. CONCLUSIONS

For cases of intrauterine fetal death or fetal anomaly from 14 to 28 weeks of pregnancy which is indicated to terminate the pregnancy. It should be used vaginal misoprostol because it has a high success rate, shortens the time of the expulsion of the fetus and its side effects. It is rarer than oral misoprostol.

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