Research Report

Efficacy of 600 μg Misoprostol compare to 400 μg Misoprostol orally for expulsion of conception mass on pregnancy failure under twenty two weeks of gestational age

Efektivitas penggunaan Misoprostol 600 μg dibandingkan dengan Misoprostol 400 μg per oral untuk pengeluaran hasil konsepsi pada kegagalan kehamilan usia di bawah dua puluh dua minggu

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Abstract

Objective: To evaluate the efficacy and adverse effect of misoprostol in pregnancy termination under 22 weeks of gestation with dosage 400 μg, in comparison to 600 μg.

Method: The research was performed in Obstetric and Gynecology Division in Dr. Cipto Mangunkusumo General Hospital to 70 subjects which were chosen with consecutive sampling, divided into two groups with block randomization and double blind. Group A received 400 μg of misoprostol every 6 hours while group B received 600 μg of misoprostol every 6 hours for a maximum of 2 days. Each group was evaluated for the time it took to reach complete abortion and for the adverse effects, consisting of abdominal cramping, bleeding, vomiting, and diarrhea.

Result: Success rate for termination with misoprostol 400 μg and 600 μg were 88.5% and 91.4%, with no statistical difference found (p=1.000). There was no difference in the time for reaching complete abortion between two dosages (p=0.701) with a mean of 22 ± 8 hours. Adverse effects were found more frequent and more severe in the group consuming 600 μg of misoprostol compared to the group receiving 400 μg of misoprostol.

Conclusion: Four hundred micrograms of misoprostol every six hour is recommended for termination of pregnancy under 22 weeks of gestational age, without statistical difference in efficacy, but with lower adverse effects.

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Keywords: misoprostol, pregnancy failure, dosage, efficacy, adverse effect

Abstrak

***Tujuan**: Mengetahui efektivitas dan efek samping penggunaan misoprostol 400 μg dibandingkan dengan misoprostol 6oo μg untuk pengeluaran hasil konsepsi pada kegagalan kehamilan usia ≤ 22 minggu.*

***Metode**: Penelitian dilakukan di Departemen Obstetri dan Ginekologi RSCM terhadap 70 subjek yang dipilih dengan cara pengambilan sampel berurutan lalu dibagi menjadi dua kelompok perlakuan dengan randomisasi blok dan ketersamaran ganda. Kelompok A mendapatkan misoprostol 400 μg tiap 6 jam selama dan kelompok B mendapat misoprostol 600 μg tiap 6 jam selama maksimal 2 hari. Dilakukan penilaian lama terjadinya ekspulsi jaringan komplit dan efek samping berupa perdarahan, kram, muntah dan diare pada masing-masing subjek penelitian.*

***Hasil**: Didapatkan angka keberhasilan untuk terminasi dengan misoprostol 400 μg dan misoprostol 600 μg adalah 88,5% dan 91,4% untuk usia kehamilan ≤ 22 minggu. Tidak didapatkan perbedaan keberhasilan yang bermakna secara statistik (p=1,000). Tidak didapatkan perbedaan waktu ekspulsi komplit antara kedua dosis (p=0,701) dengan rerata waktu tercapai ekspulsi 22 ± 8 jam. Didapatkan perbedaan bermakna pada beratnya efek samping berupa kram, perdarahan, muntah dan diare antara dosis 400 μg dibandingkan dengan dosis 600 μg, di mana efek samping lebih sering didapatkan dan lebih berat pada kelompok perlakuan dengan dosis 600 μg.*

***Kesimpulan**: Penggunaan misoprostol dosis 400 μmg lebih disarankan untuk pengeluaran hasil konsepsi pada kegagalan kehamilan usia ≤ 22 minggu dibandingkan dengan dosis 600 μg dengan efektivitas yang tidak berbeda bermakna namun efek samping yang ditimbulkan lebih sedikit.*

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***Kata kunci**: misoprostol, kegagalan kehamilan, dosis, efektivitas, efek samping*

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INTRODUCTION

Unsafe abortion is prevalent in many developing countries where abortion laws are more restrictive, the unmet need for contraception is high, and the status of women in society is low. The main interventions for reducing the prevalence of unsafe abortion are known: better and more widely available family planning services, comprehensive sex education, higher access to safe abortion and high-quality post-abortion care, including contraceptive counselling and on-site services.[1]

According to the WHO, 19 million women have illegal abortion every year and 18.5 million of these take place in developing countries.[2] The number of mortality due to illegal abortion was estimated to be around 68.000 deaths annually.[3] Medical methods offer safer alternative way compared to operative procedure.[4]

Medical abortion is a method for pregnancy termination using single – or combination – dose of oral administered drugs, vaginal medication, and/or intramuscular drugs, resulting in conception-mass expulsion. There are three medical abortion combination methods use worldwide. These are mifepriston and misoprostol, methotrexate and misoprostol, and misoprostol only.[5]

Several researches have shown that medical abortion is safe enough, effective, and has high acceptance for both the patient and caregivers.[5] The method using single misoprostol can be used in many regions which has no mifepriston available, with fine results.[5,6]

Nowadays, pregnancy termination is generally done by performing either dilatation and curetation. Meanwhile, the absolute regimen in pregnancy termination using medical method is not yet to be discovered. In literature, using 600 μg of isoprostol trough buccal mucous in less than 12 weeks of pregnancy has a success rate of 86%.[5-7] There is no established recommendation for termination of pregnancy in 13 -22 weeks using oral misoprostol. Higher dosage is needed during the administration of oral route compared to other routes in order to produce similar effect. However, oral route is the most acceptable and comfortable method for patients.

METHOD

The study was conducted after FKUI ethical commission approval had been obtained, and the samples were collected from January to September 2009. The method of the study was Randomized Controlled Clinical Trial with double blind approach and parallel independent design.

The sample was chosen with consecutive sampling. The study population consisted of every patient which came to our clinic with pregnancy failure. Samples were divided into two groups with block randomization. Group A received 600 μg misoprostol orally every 6 hours, and group B received 400 μg misoprostol orally every 6 hours. Both groups fulfilled the inclusion criteria and were willing to participate in the research.

Sample size was calculated with hypothetical study formula by means of two populations of independent groups. Based on the calculation, the study required 35 people for each group.

The primary outcome measured was the expulsion of conception mass. It was measured every 6 hours after given misoprostol with physical examination and transvaginal ultrasound if needed. The dose was repeated every 6 hours if a complete abortion has not been achieved. A failed induction was defined as failure to expel the conception mass completely after 48 hours or heavy bleeding occurred at which point evacuation will be done either with high dose oxytocin infusion or curetage. The time interval between induction and complete abortion were recorded.

Secondary outcome measured were misoprostol side effects, which include vaginal bleeding, abdominal cramping, nausea/vomiting, and diarrhea. Abdominal cramping were divided into 3 classes, class 1 correspond to menstrual cramping, class 2 more severe than menstrual cramping but still tolerable, class 3 heavy abdominal cramping which already disturb daily activity. Vaginal bleeding were divided into 4 classes. Class 1 spotting, class 2 correspond to menstrual bleeding, class 3 more heavy than menstrual bleeding, class 4 severe bleeding that cause the patient to worry. Diarrhea were divided into 2 classes, class 1 with frequency < 5 times/day, class 2 with frequency ≥ 5 times/day. Vomiting were divided into 3 classes. Class 1 benign (frequency < 5 times/day), class 2 medium (frequency 5 - 10 times/day), and class 3 heavy (frequency ≥ 10 times/day).

Data were analyzed using the SPSS 11.5 Statistical analyses were performed using the Chi-square test or Fischer exact test for qualitative variable and Kolmogorov-smirnov test for ordinal and dicotomic qualitative variable. $p < 0.05$ was considered significant.

RESULT

Sample collection was conducted from January 2009 to September 2009. Research sample consists of 35 subjects for each group.

Table 1. Research subject characteristic

Subject Characteristic	Group		p value
	400 μg (n=35)	600 μg (n=35)	
Age Group			
<21 Yo	7	4	
21-30 Yo	17	19	0.16
>30	11	12	
Academic Background			
SD/SMP	7	11	
SMA	21	17	0.519
College/Above	7	7	
Occupation			
Housewife	24	27	0.591
Carier Woman	11	8	
Parity			
Primi	17	14	0.630
Multi	18	21	
Indication			
BO	9	8	
Conceptus			
Demise	14	17	
MCA	2	3	0.430
Missed/Retain			
Conception	3	5	
IUFD	7	2	

Subject age in this research ranged from 17 - 45 years old with average age is 29 years old and most of subjects (51.4%) are included in the group age of 21 - 30 years old. Most subject's academic background were high school (54.2%) and most of them were housewives (72.8%) and also most of these subjects were multiparity (55.7%).

The conception demise is the leading indication for pregnancy termination in this research, followed by blighted ovum (44.2% and 24.2%).

Equality review was performed on subject characteristic and the indication for pregnancy termination between group with 400 μg misoprostol and 600 μg, whereas no significant differences were found on the research subject (p>0.05)

Table 2. Efficacy for each research group

Misoprostal dose	Succeed	Fail	p
400 μg	31	4	1.000
600 μg	32	3	

The results showed that the use of 400 μg and 600 μg of misoprostol orally every 6 hours for pregnancy termination below 22 weeks of gestational age, had a high success rate (88.5% and 91.4%). No significant differences in the success rate for termination in both groups with p = 1.000 (fisher exact) and RR = 1.03 (0.88-1.21). (Table 2)

Table 3. Complete expulsion time

Misoprostal dose	Expulsion		p
	≤ 24 Hour	24-48 Hour	
400 μg	31	4	1.000
600 μg	32	3	

Out of 63 subjects, the average expulsion time needed was 22 hours ± 8 hours - with 6 hours as the shortest expulsion time and 32 hours as the longest period for expulsion to happen. Another finding was that in the group of 400 μg of misoprostol, 45.1% of subjects reached expulsion point in less than 24 hours compared to 50% of the subjects in the group who were given 600 μg of misoprostol. No significant differences was found between 400 μg misoprostol and 600 μg group with p value = 0.701 and RR = 0.824 (0.306-2.217) in term of time needed for complete expulsion. (Table 3)

Table 4. Adverse effect on both groups

Adverse effect	Group		p Value
	400 μg (n=35)	600 μg (n=35)	
Abdominal Cramp			
Equal to menses	2	0	0.000 (KS)
>Menses	32	14	
Disturb daily activity	1	21	
Bleeding			
Equal to menses	18	3	0.003 (KS)
>Menses	17	21	
Causing anxiety	0	11	
Vomit			
None	24	3	0.003 (KS)
<5 Times	11	31	
5-10 Times	0	2	
Diarehea			
None	15	4	0,003*
<5 Times	20	31	

KS: Kolmogorov-Smirnov
**: chi square*

We also found that most of the subject complained of abdominal cramp exceeding usual menstrual period (65.7%), but the disturbing abdominal cramping was most likely found in the subject group of 600 μg of misoprostol (60%) compared to the group of 400 μg of misoprostol (2.9%).

Bleeding complaints in 400 μg misoprostol group mostly resembled the amount of blood secreted during menstruation (51.4) whereas the subjects in 600 μg misoprostol group complained of bleeding in larger amount than that in menstruation period (60%). Most of the subjects in study group who were given 600 μg misoprostol experienced vomiting <5 times/day (88.6%), whereas the same complaint were only found on few patients of 400 μg misoprostol group. Diarrhea with less than 5 times/day in the group of 400 μg misoprostol were only found on 20 subjects (57.1%) while in the group of 600 μg misoprostol, this complaint was found on 31 subjects (88.6%) Statistical analysis from all of the complains above found that p-value for each of them was 0.000; 0.003; and 0.000 for cramping, bleeding, and vomiting - using the Kolmogorov-Smirnov calculation. For the diarrhea, the p-value was 0.003 with Chi-Square calculation. With p < 0.05 we concluded that there was a significant difference for the side effects between both groups, in which the side effects in group with 600 mg of misoprostol were heavier than that of the 400 mg group. (Table 4)

DISCUSSION

The main purpose of this study was to figure out the efficacy and to compare the adverse effects on giving 400 μg misoprostol and 600 μg orally in order to terminate failed pregnancy below 22 weeks of gestational age. Seventy-women were randomly-chosen as subject with different socio-demographic background.

Patients were dominantly regular housewives and had already been pregnant prior to this research. Statistical review did not find any significant difference on subject characteristics between the 400 μg and 600 μg misoprostol groups, in which the similar pattern of subject characteristics was found.

Parity, gestational age, and pregnancy termination indication are factors which could affect the outcome - back in earlier days of performing such studies as this.[5,8] Complete expulsion in multiparity is much faster then first parity.[7] Nevertheless, this conclusion was denied by other research, pointing out that there are no correlation found between termination outcome and parity.[9]

In this study, the evaluation of gestational age, diagnosis, and subjective parity were not reviewed with the termination outcome because both objects matches the different types of study designs.

Based upon literature, medical termination success outcomes reach a percentage of between 70-95%.[5,7,10]

In this research, researches managed to achieve success point for 88.5% of the group with 400 μg misoprostol and 91.4% of the group with 600 μg misoprostol. With the significant analysis, we did not find any meaningful differences between the efficacy of 400 μg misoprostol and 600 μg misoprostol for less

than 22 weeks pregnancy termination [p = 1.000 and RR=1.03 (0.88 - 1.21)].

Period of time needed for complete evacuation of conception mass was noted, out of 63 samples taken, no significant differences in the time needed for complete conception expulsion was shown between the 400 μg misoprostol and 600 μg misoprostol (p=0.701 and RR = 0.824 [0.306-2.217]). The average of time elapsed of expulsion is 22 ± 8 hours.

From previous studies, it is known that the effect of using 800 μg misoprostol on second trimester continued with 400 μg orally will result in the expulsion, which took an average of 15.9 ± 2.3 hours.[11]

The difference of expulsion time was due to most of this research subject were first trimester pregnancy failure (54.3%) with the average gestational age 13 ± 4 weeks, while in previous study the average gestational age is 20.7 ± 2.1 weeks.

This matched the literature, which explained the correlation between gestational age and pregnancy termination.[5,8]

Meanwhile, in the studies which are using 200 μg, 400 μg, and 600 μg of isoprostol via vaginal route for pregnancy termination in second trimester, the side effect complaints are vomiting, diarrhea, and bleeding. No extraordinary treatments were necessary for those symptoms, only a low-dose of analgesic. Statistically, the adverse effect complaints on those who were given 600 μg are significantly different to those of other dosage groups.[12] While 800 μg via vaginal route followed by 400 μg misoprostol via oral route usually results to mild complaints which can be well tolerated by the patients.[11,13,14]

In this research, abdominal cramping which disturb daily activity had happened on 21 subjects (60%) in the group of 600 μg of misoprostol, compared to only 1 subject (2.9%) in the group receiving 400 μg of isoprostol.

This also happened with the bleeding complaints. In group of 600 μg of misoprostol, there were 11 subjects (31.4%) who complained of bleeding which made them uncomfortable, while in the other group, no such complain was found. Vomit reaching 5-10 times in 24 hours was found on 2 subjects (5.6%) in the 600 μg misoprostol group and no such complain happen in other group.

There was also an obvious clinical difference found for diarrhea. Thirty one subjects (88.6%) in 600 μg of misoprostol group complained of diarrhea less than 5 times/day, whereas only 20 subjects (57.1%) in the 400 μg of misoprostol group had the same complain. We found that not every patients complained of vomiting and diarrhea, 37.1% patients did not experience vomiting and 27.1% of patients did not experience diarrhea.

Statistical analysis was performed and similar result with previous literature was found. We found significant differences for abdominal cramping, vaginal bleeding, vomiting, and diarrhea for group with 600 μg of misoprostol compared to group with 400 μg of misoprostol (p = 0.000; p = 0.003; p = 0.000; and p = 0.003).

Previous research in the literature found that the use of misoprostol for pregnancy termination in patients with history of caesarian section until gestational age of 24 weeks is safe.[15,16]

In this research we had 2 subjects with history of caesarian section twice, and one subject with history of caesarian section once, in their early pregnancies. Subject with twice Caesarian Section (CS) history were given 400 μg and 600 μg of misoprostol while one subject with history of CS once received 600 μg of misoprostol. All of these subjects had complete expulsion of conception mass and there was no uterine rupture or severe side effects found. In order to figure out the statistical difference also safety and efficacy for misoprostol in patient with history of uterine scar, further studies with larger group studies is needed.

CONCLUSION

Administration of 400 and 600 μg of misoprostol orally every six hours for pregnancy termination in less than 22 weeks of gestational age are safe and effective.

Side effects (abdominal cramping, bleeding, vomiting, and diarrhea) are more prevalent in the use of 600 μg compared to 400 μg of misoprostol.

The use of 400 μg of misoprostol every 6 hours orally are recommended for pregnancy termination in gestational age less than 22 weeks.

Further studies with larger subject group is needed in order to figure out the statistical difference also safety and efficacy for misoprostol in patient with uterine scar.

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