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Comparison between different dose regimens of misoprostol in termination of early pregnancy

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Abstract

Objective**:** compares efficacy & side effects of vaginal put of 400 or 600 microgram of cytotic in repeated doses in termination of first trimester gestational age. Desgn: Randomized prospect study. Setting and duration of study: Maternity teaching hospital in Sulaimani from 1st of January to the end of June 2009. Patients and methods: This study was included 90 pregnant women admitted during first trimester of gestation, requiring termination of pregnancy because of fetal demise. These patient are divided into two groups: (45) women received 600 mcg of misoprostol vaginally and other group 45 were received 400 mcg of it also vaginally. Misoprostol was given every 6hr for three doses. They were observed and evaluated in 24 hours.Result: Group1 had a complete abortion rate of 35.6% while group2 abortion rate of 13.3% this was significant. The time interval from put abortion was 8.04 ± 4.280 hours in group1 and 9.62 ± 5.237 hours in group2. Side

	effects such as diarrhea, nausea and headache showed no statistically significant difference in both patients.

المقارنة بين أنظمة الجرع المختلفة للميزوبرستول في إنهاء الحمل المبكر

فتحية مجيد هناء العاني سراب صالح جاسم

الخلاصة

الهدف: أجريت هذه الدراسة لمقارنة فعالية واهم التأثيرات الجانبية لعقار الميزوبروستول عند إعطائه عن طريق المهبل بواسطة جرعتين ٦٠٠ او٤٠٠ مايكرو كرام لإنهاء الحمل الذي مدته ١٣أسبوع او اقل. التصميم: دراسة مستقبلية عشوائية. مكان الدراسة: مستشفى الولادة التعليمي في السليمانية في الفترة مابين الأول من شهر كانون الثاني الى نهاية شهر حزيران. طريقة العمل: شملت الدراسة (٩٠) امرأة حامل في الأسابيع الثلاث عشرة الأولى من الحمل و تحتاج إلى إنهاء الحمل بسبب موت الجنين داخل الرحم أو تشوهات في الجنين ,تم تقسيم نموذج الدراسة إلى مجموعتين: المجموعة الأولى شملت(٤٥)امرأة حامل أعطيت لها عقارالميزوبروستول عن طريق المهبل بجرعة ٦٠٠ مايكرو كرام كل ست ساعات لحد ثلاثة جرع ,المجموعة الثانية شملت(٤٥) امرأة حامل أعطيت لها العقار نفسه بجرعة ٤٠٠ مايكرو كرام عن طريق المهبل أيضا وتم مراقبة الحوامل لمدة ٢٤ ساعة من وقت وضع العقار حتى حدوث الإسقاط. النتائج: نسبة الإسقاط الكامل في المجموعة الأولى٦.٣٥ %, و ٣,١٣% في المجموعة الثانية وكانت نتيجة احصائياً ذو أهمية ملحوظة ,أما متوسط الفترة اللازمة لحدوث الإسقاط في المجموعة الأولى كان٠٤.٨ , وكانت ٩ .٦٢ في المجموعة الثانية. إن الأعراض الجانبية لكلتا المجموعتين كانت تقريبا متساوية ولا يوجد فرق مميز بينهما وكانت احصائياً غير ذو أهمية. ألاستنتاج: أظهرت الدراسة أن إعطاء عقار ميزوبروستول بجرعة ٦٠٠ مايكرو كرام عن طريق المهبل لإنهاء الحمل أكثر فعالية من إعطائه بجرعة ٤٠٠ مايكرو كرام.مع العلم لم يكن هناك أي اختلاف للإعراض الجانبية بين المجموعتين.

Introduction

Termination (or abortion) is the medical process of ending a pregnancy so it does not result in the birth of a baby. Surgical methods is used for early pregnancy abortion since antiquity. Cervical ripening agent, surgical complications were reduced. The rate of these complications, is between 4% and 10% which include perforation of uterus, injuries of cervix and hemorrhage [1,2]. The majority of indication for termination include chromosomal abnormalities of the embryo or fetus, other hormonal problems, infection, and abnormalities of the uteru[3]. Of all recognized pregnancies, 15-20% end spontaneously in the first and second trimester[3]. Induction of abortion needs effective care, like women with child birth [4]. Among these options misoprostol as the agent of choice for termination of gestational age caused by intrauterine fetal death or gross malformation[4]. The use of prostaglandins appears as safe and effective in end of pregnancy. In the beginning prostaglandin E2 was commonly used, however, as its cost was quite high, its usage was declined. Synthetic prostaglandins E1 has been introduced with a lower cost and fewer complications [5,6].

Miscarriage :-

The natural death of an embryo or fetus before it is able to survive independently. The most common symptom of a miscarriage is vaginal bleeding with or without pain. Miscarriage is the most common complication of early pregnancy**.**

Types of miscarriages :-

-Spontaneous Miscarriage :-

is the most common complication of early pregnancy. of spontaneous miscarriage occurs in approximately 15% to 20% of pregnancy.The great majority occur early before 12weeks gestation, while mid trimester loss, between 12 and 24 weeks, occurs less frequently and constitute less than 3% of all pregnancy

outcomes. Type of spontaneous miscarriage[7].

A-Threatened miscarriage: Describes any bleeding during pregnancy, prior to viability, that has yet to be assessed. At investigation it may be found that the fetus remains viable and the pregnancy continues without further problems, about 1/4 of all pregnancy are complicated by threatened abortion, bleeding usually resolves spontaneously within few days and cervix is closed not dilated [26].

B-Recurrent miscarriage: When there is three or more consequent spontaneous miscarriage may present clinically as any of previous forms of abortion [7].

C-Silent miscarriage. Is when the embryo or fetus has died, but a miscarriage has not yet occurred. It is also referred to as delayed miscarriage, silent miscarriage, or missed abortion.

D-Incomplete abortion: occurs when some products of conception have been passed, but some remains inside the uterus. The fetus and placenta may partially extrude through dilated os[27].

Termination of pregnancy: Termination can be performed either surgically or medically:-

1- Surgical and mechanical termination :-Pregnancy may be ended surgically by an appropriate dilated cervix, or trans-abdominally by either hysterotomy or hysterectomy [10].

1-1 ***Vacuum aspiration*[28]*.***

1-2-hygroscopic dilators.

2- Medical termination in first trimester: Medical termination include the use of followings:

A-Mifepristone: Mifepristone aderivative of norethindrone, binds to the progesterone receptor with an affinity greater than progesterone itself but does not activate the receptor, thereby acting as an antiprogestin. Its known actions on a uterus in pregnant women include decidual necrosis, cervical softening, and increased uterine contractility and prostaglandin sensitivity [8].

B-Prostaglandins:

These are long chains fatty acids derived from Arachadonic acid via the cyclooxygenase pathway[11]. Prostaglandins acts on cervix and myomatrium throughout pregnancy. prostaglandins enable to ripe the cervix by many mechanisms, the extra cellular substance of cervix and prostaglandin E2 increase the activity of collagenas [12,13].

C-Misoprostol: Misoprostol is the generic form of the brand-name drug Cytotec, which is used to prevent ulcers in people who take certain arthritis or pain medicines. Misoprostol is a synthetic prostaglandin. It works by protecting the stomach lining and decreasing stomach acid secretion.It is sometimes used off-label to end an early pregnancy.

Pharmacokinetic of cytotec: Misoprostol, a prostaglandin analogue, binds to myometrial cells to cause strong myometrial contractions leading to expulsion of tissue. This agent also causes cervical ripening with softening and dilation of the cervix. Misoprostol binds to and stimulates prostaglandin E1 receptors, prostaglandin EP3 receptor and prostaglandin EP4 receptor but not Prostaglandin EP1 receptorand therefore is expected to have a more restricted range of physiological and potentially toxic actions than prostaglandin E2 or other analogs which activate all four prostaglandin receptors [17].

Indication and uses of misoprostol: sold under the brandname Cytotec among others, is a medication used to start labor, cause an abortion, prevent and treat stomach ulcers, and treat postpartum bleeding due to poor contraction of the uterus. For abortions it is often used with mifepristone or methotrexate. By itself effectiveness for this purpose is between 66% and 90%.[3] It is taken either in the cheek, under the tongue, or placed in the vagina[18]. side effect of misoprostol: The most common adverse

effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chill, shivering and fever. Less frequently reported adverse effects include: fatigue, rash, and body ache. Other effects especially when used in women (for treatment of ulcer) are abdominal cramp and vaginal bleeding [14,19,20].These side effects are dose related, usually transitory and well tolerated .Uterine rupture has been reported with misoprostol used for termination in the 2nd trimester with or without previous C/S [20]. Toxic doses of misoprostol not known,

Teratogenicity of cytotec:- Misoprostol is known to induce congenital anomalies in the fetus when given in the first trimester, the most frequent anomalies are equinovarus (clubfoot) followed by anomalies of the cranial nerves (V, VI, VII, XII) and ageneses of the fingers [12,21].

Caution and contraindication of misoprostol:- The main contraindications are pregnancy and breast feeding (possible diarrhea of infant, and hypersensitivity to misoprostol). Misoprostol should be used with caution in cases with hypotension because it might precipitate severe complication, e.g.: cerebrovacular accident and cardiovascular accident [12].

Patients and Methods

This randomized trial was conducted in sulaimani maternity hospital during the period from 1st of January to the end of June 2009 to compare the efficacy of 600 Mcg versus 400 Mcg of misoprostol vaginally in termination of 1st trimester of pregnancy in case of blighted ovum, fetal demise in utero. The present study recruited 90 pregnant women with gestational age 13 weeks and less were randomly allocated into two groups. All women included were informed of the nature and scope of the study and verbal consent was obtained from each, prior to participation in the study. After admission complete history including; age, parity, gestational age, history of present pregnancy was taken. Base line investigations, especially hemoglobin concentration, PCV, blood groups and Rh. factor were performed and patients with Rh negative were given anti D after abortion. Gestational age was assigned on the bases of either menstrual date with confirmatory early ultrasound or early ultrasounds alone when menstrual date uncertain.The pregnant women with a history of drug allergy, pulmonary and cardiovascular disease, blood disorder, molar pregnancy were excluded from the study.The selection of 90 cases that were scheduled for termination of pregnancy for either 400Mcg or 600Mcg was done randomly. The 1st 3 days of the weeks were used to termination by 600Mcg until 12 pm. The next 3 days of the weeks termination were done by 400Mcg until 12pm.

The two groups were:-

Group1, includes 45 patients received 600Mcg of misoprostol every 6 hours for three doses per 24 hours.

Group 2, included 45 patients received 400Mcg of misoprostol every 6 hours for three doses. Both groups received misoprostol vaginally. The patients were restricted to bed for at least 20 minutes after drug application and clinical signs and complications were observed closely for the next 24 hours. The clinical condition of patients with complete abortion were closely observed. An U/S was arranged after abortion to exclude retained product of conception and Hb, PCV was checked also. In cases of incomplete abortion which was proved by U/S, curettage was performed. Another u/s was done for them after curettage to exclude any retained pieces of conceptus. Patients were asked to come 1 week after discharge to check for signs and symptoms of infection and to report any other complications.The patients who had excessive bleeding and PCV was less than 30% wereconsidered for blood transfusion. The initiated abortion was observed from the time of misoprostol application to the posterior fornix of vagina until the time of expulsion of the

conceptus. The side effects of misoprostol were observed including, diarrhea, nausea, vaginal bleeding, and headache. The data were analyzed using chi-square test, Student t-test, arithmetic mean and standard deviatiation. The interpretations of the results were done through the measurement of P value with statistically significant effect when P value is less than 0.05.

Results

During the six month period of this study a total of 90 patients, were taked; 45 patients of 600 Mcg cytotec and 45 patients of 400Mcg misoprostol. Patients' data demonstrated in Table 1, different variables include (age, weight, parity, gestational age) of both groups. No statistical difference were found between both groups.

Table (1):- Patients characteristics

Parameters	Group 1 Mean ± SD	Group 2 Mean ± SD	P value
Age(year)	29.7±4.9	30.08±5.01	0.717
Weight (Kg)	66.56±5.02	64.95±4.49	0.104
Gestational age (weeks)	8.53 ± 2.332	9.07± 2.016	0.249
Primigravida **Para 1+**	16(35.6%) 29(64.4%)	15(33.3%) 30(66.7%)	0.825

Table (2) Abortion rate within 24. Significantly higher complete abortion rate in patients taking 600 Mcg of cytotec (35.6%) compared with patients those taking 400 Mcg of cytotec (13.3%) and p value 0,014.

Table (2):- Rate of abortion in 24 h.

Type of abortion	Group1	Group2	P value
Complete	16(35.6)	6(13.3)	
Incomplete	29(64.4)	39(86.7)	**0.014**

Table (3) the mean time interval for abortion. The Mean ± SD of time interval after insertion of misoprostol to complete and incomplete abortions were 8.04 ± 4.280 versus 9.62 ±5.237 for both groups respectively and this was not stastically significant(P=0.121).

Table (3):- Induction to abortion time in both groups.

Mean time of abortion(hours)	**Group1** **Mean ± SD**	**Group2** **Mean ± SD**	P value
	8.04 ± 4.280	9.62 ±5.237	0.121

Table (4) the side effects of cytotec within 24 hours after administration., In group (1) there was no significant side effect in about(93.3%), diarrhea about (2.2%), nausea about (4.4%). In group (2) side effect about(93.3%) was nil and headache about (2.2%). There was no statistical significant between both groups P= 0.199.

Table (4):- Side effect of misoprostol within 24 h. in both groups.

Side effect of misoprostol	Group 1 N(%)	Group 2 N (%)	p- value
Nil	42(93.3)	42(93.3.)	0.199
Diarrhea	1(2.2)	0(0.0)	
Nausea	2(4.4)	0(0.0)	
Headache	0(0.0)	1(2.2)	

Table (5) the number of tablets of misoprostol used for termination of pregnancy in both groups. In group (1) 28 women aborted after one tablet while in group (2)13 women and 12 women in group (1) aborted after two tablet versus 19 in group (2). In group (1) only 5 women received three tablet while in group (2) 13 women used it. The difference was statistically not significant P=0.230.

Table (5):- Frequencies and percentages of number of

No. of tablets	Group 1		Group 2		P value
	No.	%	No.	%	
One tablet	28	62.2%	13	28.9%	0.230
Two tablets	12	26.7%	19	42.2%	
Three tablets	5	11.1%	13	28.9%	

Table (6) demonstrates the difference in PCV before and after abortion in both groups .The Mean ± SD of PCV before abortion was 35.0±3.05 in group1, while in group 2 was 35.6±3.7 and the Mean ± SD of PCV after abortion was 33.7±2.9 in group1 while in group 2 was 34.2±3.4 .There were no statistical significant in PCV before and after abortion between botroups**.**

Table (6):- PCV before and after abortion in both groups

PCV	Group 1 Mean ± SD	Group 2 Mean ± SD	P value
Pre-abortion	35.0±3.05	35.6±3.7	0.407
Post-abortion	33.7±2.9	34.2±3.4	0.476

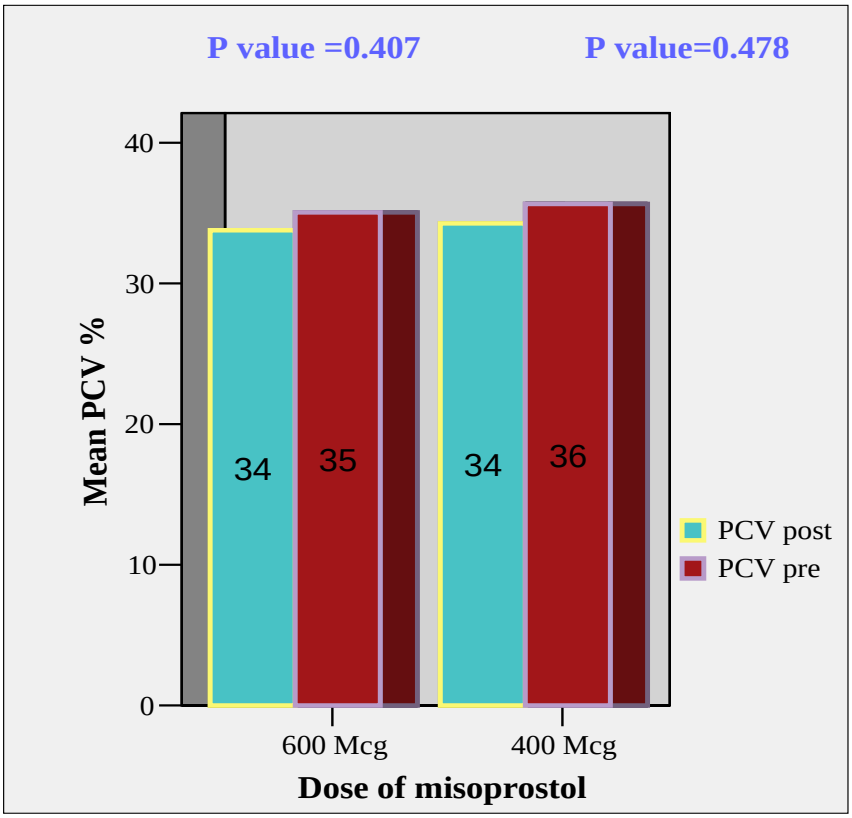

Fig. (1):- The mean of PCV before and after abortion in the two groups there s no significant difference statistically

Disscussion

The main advantage of medical abortion is that it allows women to avoid the risks of surgery and anaesthesia. In this prospective study, we found that medical termination of pregnancy using vaginal misoprostol alone was 96% effective in women with early pregnancy. Misoprostol can be taken vaginally,

orally or in combination in different dosages. In this present study, we compared the vaginal 600Mcg versus 400Mcg of misoprostol regarding type of abortion, side effects and induction-abortion interval. The complete abortion rate was observed at significantly higher number in group1 (35.6%) compared to group2 (13.3%). Wibool Ruangchainikhom et al showed a higher rate of complete abortion (56.9%) when using 600 Mcg compared to a lower rate of complete abortion (38.3) when using 400Mcg,this study agree with the present study, Wibool Ruangchainikhom et al were taken 125 pregnant women while in present study was 90 pregnant [(22)]. Josep L. et al. agree with our study regarding the rate of complete abortion as they reported (98.1%) complete abortion rate in the 600Mcg group and(94.3%) in the 400Mcg group, Josep L. et al study which used 105 pregnant women in each group [(23)]. However, the result of present study disagree with Singh, K et al who reported a lower complete abortion rate when using 600Mcg (16.7%) compared with higher rate in using 400Mcg(30.3%) when they were taken 60 pregnant women (24). Regarding the mean time interval in the present study, the mean time for abortion was 8.04± 4.280 when using (600Mcg) regimen and 9.62± 5.237 when using (400Mcg) regimen, this was not statistically significant P=0.121 which agrees with Wibool Ruangchainikhom et al. study which showed that time interval after insertion of misoprostol to complete abortion has not statistical significant difference between bothe groups,8.85± 4,68 when using 600Mcg and 9.15± 6.09 when using 400Mcg P=0.165 [(22)]. Also, Josep L et al. agrees with our study regarding times interval which showed the rate of time interval about 10,7±1.3 in 600Mcg and 11.5±5.0 in 400Mcg which was not statistically significant (P=209)[(23)].The present study agrees also with Singh, K. in time interval which was about 3hours in 400Mcg group and 2hours in 600Mcg group there was no statistical significant difference P=0.654 [(24)] .In the present study there was no statistical significant difference between both groups in side effects (P=0.199). This also agrees with Wibool Ruangchainikhom et al study regarding the side effects of misoprostol when using 600Mcg about (43%)lower abdomen pain, excessive vaginal bleeding (18%), diarrhea (3%) and fever(6%), and the side effects of misoprostol when using 400Mcg were about(40%)lower abdomen pain, excessive bleeding (16%), diarrhea (3%) and fever(5%). There were found no statistical significant difference (P=0.373) in WiboolRuangchainikhom et al study [(22)]. Ayres et al disagrees with present study in side effect of misoprostol when using 600Mcg, they were reported about (5%) vomiting and (6%) fever while the present study was reported nausea(2,2%) and diarrhea about (4,4%) [(25)]. Singh, K. et al. disagrees with our study regarding side effects which showed there is increase side effect in 600Mcg such as vaginal bleeding, abdominal pain, fever of greater than 38.0 degree when compared with 400Mcg group [(24)]. In the present study excessive vaginal bleeding was observed in two patient.

Conclusions

The present study shows that misoprostol is effective for in termination of early pregnancy with an acceptable rate of success. Vaginal cytotec 600 microgram is higher rate than 400 microgram in end of first trimester of pregnancies inducing complete abortion without differences in side effects of both groups.

Recommendations

1- Since different regimen of misoprostol had been used for first trimester pregnancy termination, larger well designed study may be needed to established the optimal dosage regimen comparing high doses.

2-We recommend to use this medical option for termination of 1st trimester of pregnancy instead of surgical method as it is effective with little side effects and complication.

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