Use of Misoprostol to Terminate Midtremester Pregnancy

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Abstract

Objective: Our aim was to compare the effectiveness of oral versus vaginal use of misoprostol (under a protocol approved before), and the use of misoprostol for this purpose not according to this protocol (target that emerged during the implementation of the paper).

Materials and Methods: Patients determined by consultations abortion in the second quarter for the period April 2004 - June 2006 were included in the study (N = 118). Ninety one patients were randomized to protocol of vaginal or oral used misoprostol doses of 400 mcg every 4 hours. On the other hand, some cases (N = 27) underwent individual judgment and level of knowledge of the members of the medical staff. Cases prosecuted under the protocol were followed for 48 hours. Further, these cases underwent the trial of the person responsible. The main outcome of interest was the time from the induction to the expulsion . Mann-Whitney test was used to compare the average age, parity, weight, gestational age, the time of the uterus evacuation and the number of doses in the group treated according to the protocol (oral or vaginal misoprostol) versus the group treated out of protocol. The Fisher exact test was used to compare the duration stay and causes in the two groups of the study. For both statistical tests used, the values of P <0:05 were considered statistically significant.

The results: Of the 91 patients who were randomized, 42 took vaginal misoprostol and 49 took oral misoprostol, while 27 underwent not according to the protocol. The three groups were comparable with regard to age and weight of the mother, parity, indication for termination of pregnancy, and the gestational age. The average interval from induction to the fetal expulsion was shorter for those patients who took vaginal misoprostol compared to the oral route (14:29 hours versus 16.98 hours P <0:01) . The interval between induction and the fetal expulsion was shorter for those patients who had received vaginal or oral misoprostol compared with subjects treated not according to the protocol (15.63 hours versus 29.83 hours, P <0:01). Also, the number of used doses was lower in the vaginal treated group versus the oral one (3:45 unit to 4:57 unit P <0:01) and under the protocol against non according to the protocol (6:56 units versus 4.01units, P <0.001). The hospitalization time was shorter in the vaginal group. Significantly, more patients in vaginal group had the expulsion in within 24 hours. There was an increase in febrile condition but that did not match with the increasing use of antibiotics, and the condition was resolved post-partum without further complications.

Conclusions: Administration of vaginal misoprostol results in a shorter interval from induction to the expulsion of the fetus compared to the oral route and this is true for the

use of misoprostol according to the protocol compared with its use not according to protocol. The short duration of stay it means an improvement for the patient care.

Introduction. In the termination of pregnancy in the second quarter, misoprostol offers an effective alternative compared with the surgical option cervical dilation and extraction of the fetus. So many studies have as their object the use of misoprostol comparison with other traditional methods of inducing abortion in the second quarter, while the regime still tends to adequate dosage and in terms of road use of misoprostol. **Zieman et al**[3] have demonstrated that misoprostol quickly absorbed when taken oral, resulting in high initial peak serum concentrations compared with its use in the vaginal route. In the vaginal use of the misoprostol, peak serum concentration is not as high, and the fall of this concentration in serum is more gradual than the one seen in oral use. Pharmacokinetic characteristics which represents misoprostol administered vaginal are associated with many benefits for the patient; a short process of abortion; small doses of the medicament to perform abortion; and with fewer side effects. The objective of this paper was to compare the efficacy of oral or vaginal misoprostol administration for inducing the termination of the pregnancy in the second quarter, and to compare the effectiveness of the use of misoprostol according to the protocol fixed ago and spontaneous use, by the staff individual recognition degree.

Material and methods

This study was conducted in the period May 2004 - July 2006 at the University Hospital of Obstetrics and Gynecology "Koço Gliozheni" Tirana, which represents a tertiary service. This study was approved by the Department of Obstetrics-Gynecology Faculty of Medicine at the UT as a part of its strategy to define clear protocols regarding the use of misoprostol in the second trimester of pregnancy in particular, and its use in daily obstetrical-gynecological practice in general.

Patients that will interrupt pregnancy in the second quarter were passed at first in an informative talk about the method to obtain their consent to be included in the study, at the time of hospitalization. Selection of patients for each protocol became successively depending on the time of submission to the clinic for an indication which required evacuation of the uterus in the second trimester of pregnancy (an oral- a vaginal without changing sequence,and also there were cases that were not in accordance with the given protocol, which made it possible to identify a group of patients in which misoprostol was used depending on the subjectivity of the medical staff.

The study involved all the patients who had an indication for the evacuation of the uterus in the termination of pregnancy in the second quarter (this set by the consultations), in addition to them, by the confirmation of hypersensitivity to prostaglandins and not excluding those patients with previous sectio-caesarea.

The patients took the misoprostol oral or vaginal. Oral misoprostol included its oral use every 4 hours from 400 μg. Vaginal protocol consisted in the administration in the posterior vaginal fornix of misoprostol, every 4 hours from 400 μg. The tablets were not wetted before use.

There aren't other auxiliary laminar methods used. At the time of the next application dose of remaining tablets in the previous application has been removed. All the parameters were observed for 24 hours under standard protocol and secondary staff was instructed to follow these parameters.

Cases of randomized trials that were derogating the protocol (whether oral or vaginal, for objective reasons; example the staff knowledge, the staff commitment, different sources of information, etc.) were set in particular account of the use of misoprostol, the group of "not according to the protocol" and they underwent statistical evaluation too.

Followed standard data during the induction of uterine activity in the second tremester: -How the diet is tolerated; -How activity is tolerated; -Vital signs treadmill; -Complete Blood Count; -Use of the perfusions; -The method used for the termination of the pregnancy.-a -oral-b-vaginal-c-not according to the protocol; -When regular contractions are present: -Nothing oral; -Glucose 5% / 0.9% or sol.NaCl 125ml / h iv; -Vital signs each hour; -Pain: -reliever used type; -Call the doctor when: -Rupture of the membranes within 2 hours; iv antibiotic to start over 38ºC temperature; -Bleeding 100 ml / h; -The abortion process not happening in 24 hours; -When abortion is imminent; -Placenta has retention for 2 hours after abortion; After abortion must start the administration of iv infusions of 50 UI oxytocin in 1000 ml of 5% glucose / NaCl solution with 100 ml / hour. This continued for 2 hours and interrupted in the healthy puerperal women; - After abortion the patient is been informed about her welfare (to RH-factor, rubella- if the patient is not immune to rubella, the vaccine is applied before the procedure).

If the patient has not had an abortion in within 48 hours is managed by the following options; to increase the misoprostol dose by using the same road management, changing the management road, proceeding with high dosage perfusion of oxytocine, or proceeding with surgical evacuation of the uterus

The results of interest were: the interval from induction to the complete evacuation of the uterus (complete abortion). Induction is considered started when the patient receives the first dose of misoprostol. The fixing time of full evacuation is when the fetus is pulled out, only in a few cases placenta and the fetus are expulsed together; it is given as the second note with interest a maternal temperature greater than 38ºC; The potential infection of the mother determined by the temperature, leukocytosis, and the need for taking antibiotics in the period after abortion; The drug side effects including nausea or diarrhea, blood loss; The need for interventional surgical, and; failure to achieve medical completion of the pregnancy.

Statistical analysis:

Mann-Whitney test was used to compare the average age, parity, weight, gestacional age, the time of the evacuation and the number of doses in the group treated according to the protocol of vaginal or oral misoprostol taken against the group treated not by the protocol. The Fisher exact test was used to compare the duration of stay and causes of the two groups in the study. For both statistical tests used, the values of P <0:05 were considered statistically material (significant).

Results

Of the 118 patients who were randomized, 42 took vaginal misoprostol and 49 took oral misoprostol, while 27 underwent not by the protocol. The three groups were comparable with regard to age and weight of the mother, parity (comparable with the average SD), indication to terminate the pregnancy, and the gestacional age (Table .1). The average interval from induction in fetal expulsion was shorter for those patients who had received vaginal misoprostol compared to the oral route (14:29 hours versus 16.98 hours P <0:01). The average interval from induction to the expulsion of the fetus was shorter for those patients who had received vaginal or oral misoprostol compared with subjects treated not by the protocol (15.63 hours versus 29.83 hours, P <0:01 (Table 2 and Graphic). Also, the number of the doses was smaller in the vaginal treated group versus the oral one (3:45 units to 4:57 units P <0:01) and under the protocol against non according to the protocol (4.01 units versus 6.56units, P <0.001) (Graphic). The hospitalization interval was shorter in the vaginal group (Table3). Significantly, more patients of the vaginal misoprostol gruop had the fetus expulsion in within 24 hours.

It was seen an increase of febrile condition but that did not match with the increasing use of antibiotics, and the condition was post-partum resolved without further complications.

Most patients underwent curettage without any clear explanation (perhaps as a vestige of previous practices and protocols).

There were no cases of maternal infections or temperature in both groups after the inervention. Side effects were infrequent and there were no differences between groups. No uterine rupture cases were detected.

Duration of stay was shorter for women who underwent the protocol group (P <0.001).

Discussion

Induction of uterine activity in the second trimester is often the method of choice to terminate the pregnancy. Many communities have no direct access to the services of a doctor able to perform surgical termination of pregnancy in the second quarter. Misoprostol has shown that it is a highly effective agent in the termination of pregnancy. The hypothesis of this study was that the vaginal administration of misoprostol will result with a short interval from induction to fetal expulsion compared with oral misoprostol administered. This was a reasonable hypothesis, because earlier and various other studies comparing vaginal and oral use of misoprostol in inducing uterine activity, showed that vaginal administration has been more effective.

Vaginal administration allows the body the opportunity to be exposed more to the active drug metabolite. Increasing the dose or shorten the interval giving the drug orally leads to an increase in side effects that can be difficulty tolerated by the patient. Misoprostol acid levels in the serum, the active metabolite of pharmacological standpoint, are not measured in this study. Previous studies with vaginal use of misoprostol for terminating pregnancy in the second quarter have used doses of 100 in 800µg at intervals of 3 to 12 hours. A result is generally considered successful when a woman has an abortion in

within 48 hours, which went from 50% to 98%. The comparison between these studies is difficult because of the differences in the used doses. Use of 400 μg vaginal misoprostol has been reported previously and at intervals of 3 to 6 hours, also with good effects. In a non randomized study which deals with comparing doses of 200,400 and 600 μg used in vaginal route every 12 hours**, O-Prasersawat**[1] and **Herabutya** found that the increased success rate of abortion within 48 hours, was associated with the increased frequency of side effects . The dose of 400 μg was chosen for this study because most of the literature refers to this as an effective dose, fewer side effects, remembering that misoprostol is a drug not licensed for use in obstetrics and gynecology.

Ho et al[2] have compared with the first use of oral and vaginal misoprostol that preceded the use of mifepriston. With a dose of 200 μg every 3 hours by the two ways of administration, they found that the time from induction to abortion was shorter than that observed in this study, even with higher misoprostol doses. It makes you think that mifepriston acts as a pre-induction agent.

Gilbert and Reid[1o] finally report their strong expertise with a similar small group comparing the use of oral or vaginal misoprostol in the termination of the pregnancy in the second trimester. No additional medications were used as mifepriston. Dosage was not identical but results to, were more or less similar.

Demographic data of the two groups had no difference with regard to the gestacional age, parity or the indication for the completion of the pregnancy. These data are important as uterus becomes more sensitive to the utero-tonic agents with increasing of gestacional age. This is demonstrated by the escalated effective misoprostol doses by the gestacional age . In the first quarter, doses of 800 μg are recommended, while in terms of birth, induction is achieved for doses of 25 and 50 μg. It is also known that the induction of the birth is easier to be achieved compared in primiparous versus multiparous. On the other hand the induction of labor is easier if the fetus has died.

The interval from induction in a given expulsion was important to be analyzed. This interval for 48 hours was followed by further reassessed of the case for the position to be held.

No uterine rupture is registered, regarding the higher risk for uterine rupture that associates the use of PG, in inducing birth in general and misoprostol in particular. However , are observed cases of uterine ruptures in the second trimester under misoprostol action, understood quite less than in use in terms of misoprostol.

Conclusion

Vaginal misoprostol administration realizes the pregnancy completion in the second quarter faster than when given oral. This effect is due to the pharmacokinetic properties of vaginal administration. When the process of termination of pregnancy can be performed without increasing the complications, that it means an improvement of the patient care.

Table 1:: Distribution of clinical factors under medication use

method of applying misoprostol for the evacuation of the uterus	**Women age (years)**				**Women weight (kg.)**			**parity**		
	Nr.	**average**	**SD**	**P**	**average**	**SD**	**P**	**average**	**SD**	**P**
400µg vaginal every 4h	42	29.45	6.18	**0.70**	60.12	9.63	**0.83**	1.21	1.35	**0.98**
400µg oral every 4h	49	28.35	6.91		59.27	9.46		1.27	1.00	
according to the protocol	91	28.86	6.54	**0.02**	59.7	9.54	**0.83**	1.24	1.17	**0.01**
Not according to the protocol	27	25.26	6.36		59.44	6.88		0.56	1.05	
In Total	**118**	**28.03**	**6.67**		**59.61**	**8.94**		**1.08**	**1.17**	

Method of applying misoprostol for the evacuation of the uterus	**Parity**				**Gestational age (weeks)**			**Uterus dimentions (weeks)**		
	Nr.	**Mesatarja**	**SD**	**P**	**Mesatarja**	**SD**	**P**	**Mesatarja**	**SD**	**P**
400µg vaginal every 4h	42	1.81	1.77	**0.93**	19.19	3.76	**0.23**	19.49	5.32	**0.09**
400µg oral every 4h	49	1.94	1.81		18.43	3.94		17.55	3.84	
according to the protocol	91	1.87	1.79	**0.01**	18.81	3.85	**0.30**	18.52	4.58	**0.11**
Not according to the protocol	27	0.74	1.26		19.96	3.79		19.46	3.62	

In Total	**118**	**1.62**	**1.74**		**19.05**	**3.85**		**18.68**	**4.45**	

Table 2. Evacuation time and the number of doses used not/according to the protocol used for the evacuation of the uterus

method of applying misoprostol for the evacuation of the uterus	Evacuation time (h)				The number of used doses		
	Number	**average**	**SD**	**P**	**average**	**SD**	**P**
400µg vaginal every 4h	42	14.2926	18.2618	**<0.01**	3.45	2.10	**=0.02**
400µg oral every 4h	49	16.9822	9.2005		4.57	2.25	
according to the protocol	91	15.635	13.73	**<0.01**	4.01	2.17	**<0.01**
Not according to the protocol	27	29.8352	17.0695		6.56	2.93	
In total	**118**	**18.9658**	**15.9089**		**4.63**	**2.62**	

Grafic.1 The evacuation time

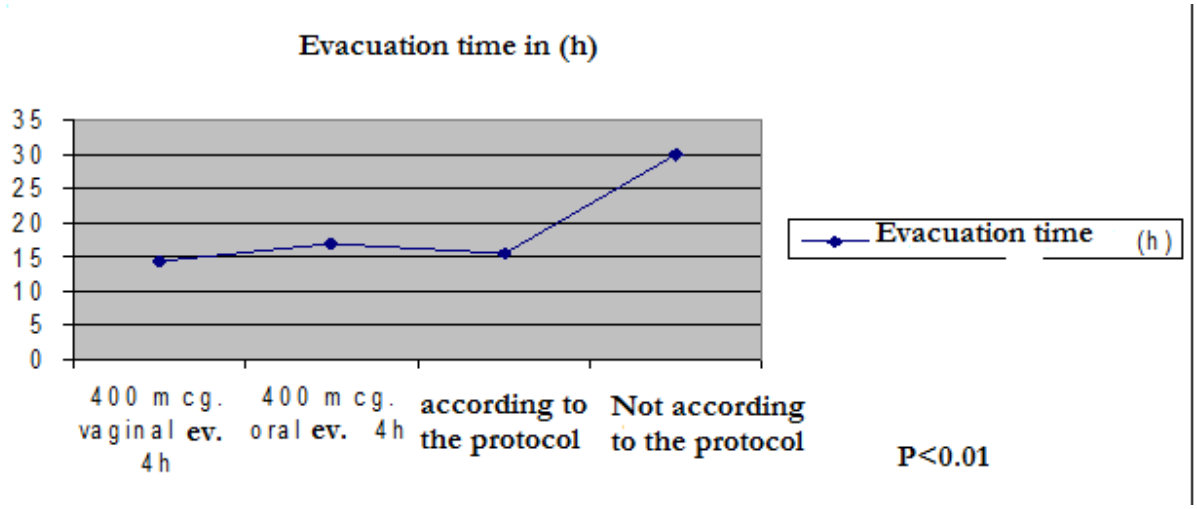
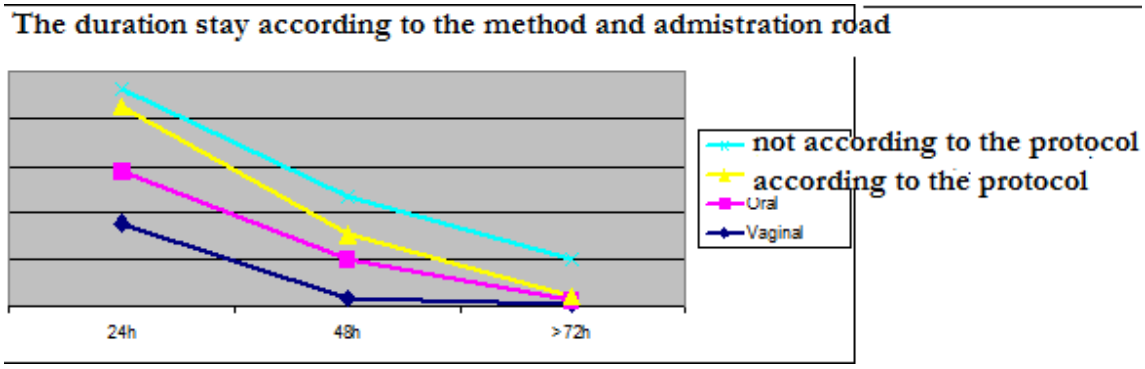


Table 3. Duration of saty in the function of the protocol used for uterus evacuation

duration of stay	**400µg vaginal every 4h**	**400µg oral every 4h**	**P**
24h	37 (88.09%)	27 (55.10%)	

48h	4 (9.52%)	20 (40.81%)	**<0.01**
≥72h	1 (2.4%)	2 (4.1%)	
In total	42 (100%)	49 (100%)	
duration of stay	**according to the protocol**	**Not according to the protocol**	**P**
24h	64 (70.32%)	5 (18.5%)	**<0.01**
48h	24 (26.37%)	11 (40.7%)	
≥72h	3 (3.29%)	11 (40.7%)	
In total	91 (100%)	27 (100%)	

Grafic 2. The duration stay according to the method and administration road



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