A PROSPECTIVE RANDOMEZED CONTROLLED TRIAL OF TWO REGIMENS OF VAGINAL MISOPROSTOL IN SECOND TRIMESTER TERMINATION OF PREGNANCY

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Abstract- The search continues for a safe effective and cheap method for mid-trimester termination of pregnancy. Misoprostol is a strong contender in this respect. The dose schedule is still not fixed. The objective of this study was to compare the efficacy and adverse effects of two dose regimens of vaginal misoprostol for second trimester termination. Prospective randomized double blind controlled trial was undertaken in 162 women at 14-24 weeks gestation in a teaching hospital. Subjects were randomized to receive either regime A: 400 µg of intra vaginal misoprostol every 6h, or regime B: 200 µg of intravaginal misoprostol every 6h. The main outcome measure was the success rate at 24h, total dose required, induction-abortion interval and adverse effects. Data was analyzed by student's t-test, Mann-whitney U-test, the chi-squared test or Fisher's exact test. There was a significant difference in the success rate at 24 and 48hr (regime A: 74% and 97.5%; regime B: 61.7% and 88.9% *P*=0.016 & 0.029 respectively) and in the mean induction abortion interval (14 Vs 20h, *P*=0.01) Mean Misoprostol requirement was significantly higher for regime A (731 µg ± 362 µg vs. 531µg ± 357µgm, *P*=0.001). Use of 400 µg vaginal misoprostol is superior to 200 µg vaginal misoprostol for second trimester abortion.

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INTRODUCTION

Recent advances in prenatal diagnosis have made possible the early detection of severe fetal conditions that maybe considered for pregnancy termination depending on the law limitations of each country. Most uterine evacuations for mid-trimester termination of pregnancy are carried out medically due to the potential complications associated with surgical termination, indeed medical terminations are used to provide a fetal specimen suitable for pathological evacuation when termination is due to a fetal abnormality. Misoporostol with or without mifepristone, has been investigated for mid-trimester medical termination of pregnancy. Although mifepristone may shorten induction abortion interval it is expensive therefore there is a need to develop an effective misoprostol alone regimen. Misoprostol, a prostaglandin analog, is the most promising of these agents because it has several advantages over other prostaglandins, including low cost, easy storage at room temperature and a favorable side effect profile.(2) Different doses, routes and regimens for medical termination of pregnancy during second trimester have been studied (3-7). Previous studies have demonstrated greater efficacy with vaginal misoprostol versus oral misoprostol (8-10). Various

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dose schedules of vaginal misoprostol have been studied for second trimester termination of pregnancy. However, to date, the optimum dose for effective termination (acceptable success rate and short induction termination interval with minimum side effects) is yet to be decided. The purpose of this study was to compare the effectiveness and adverse effect profile of two different regimens of vaginally administered misoprostol for second-trimester termination of pregnancy.

MATERIALS AND METHODS

A total of 162 healthy women carrying singleton pregnancy, admitted for legal second-trimester termination of pregnancy (14-24 week) because of IUFD, PROM, maternal medical disorders and lethal fetal congenital malformation under the license of Iranian medical legal department were recruited. The study was undertaken in the department of obstetrics and gynecology, Shariati Hospital, Tehran university of medical sciences, Tehran, Iran, during the period June 2005 – March 2007. The university ethic committee approved the study design. Inclusion criteria included: 1. all induced abortions because of IUFD, PROM, maternal medical disorders and lethal fetal congenital malformations under the license of Iranian medical legal department during 14-24 weeks of gestation, 2. an ultra sound report of existing disorders and gestational age, 3. Bishop score < 4.

Exclusion criteria included: 1.induced abortion at gestational ages rather than 14-24 weeks of pregnancy and 2. ≥2 previous cesarean sections. After proper counseling in the obstetric department, medical and gynecological histories were taken and informed consent obtained. Blocked randomization was performed with a computer-generated random number table, assignments were placed in sealed, serially numbered opaque envelops. Patients were allotted through randomizations to two different dose regimens. Group A was given 400 µg of intravaginal (in posterior fornix) misoporostol every 6h up to 6 such doses. Group B was given 200 µg of intravaginal misoprostol every 6h up to 6 such doses. Only the nurse staff was aware of dosage and neither the physician nor the patients were aware of the dose administered and the total dose was charted by the nurses separately. Scheduled assessment was carried out by the same physician every 6h by clinical and per vaginal exam. Primary outcome measure was success rate at 24h. A failed procedure was defined as failure to delivery by 48h from the first administration of prostaglandin, secondary outcome measures included the total dose of misoprostol and adverse effects such as abdominal pain, fever (oral temperature>38'C), nausea, vomiting and diarrhea. Analgesia was provided at the patient's request by intramuscular pethedine (75mg), with intramuscular metoclopramide (10mg) as the standard anti emetic medication. Post-abortion curettage was performed at the direction of the physician if the placenta had not delivered within 2 hours after the delivery of fetus.

Differences in continuous variables were analyzed by student's T-test for normally distributed data, and Mann-Whitney U-test for skewed data. The chi-squared test or Fisher's exact test was used to compare categorical data when appropriate and P-value <0.05 was considered statistically significant.

A sample size of 81 subjects in each group was calculated to have a power of 80% at 5% significance level, to detect a difference of 20% in successful delivery rate in the first 24h between the two groups.

RESULTS

A total of 81 subjects were recruited to group A and 81 subjects to group B. No significant statistical differences were observed in terms of maternal age, parity and gestational age between the two groups (Table 1). Out come measures are summarized in Table 2. Induction-abortion interval in group A was significantly shorter than group B(14 Vs 2h, P=0.01). The mean quantity of misoprostol required in group A was significantly more than that required in group B (731 ±362 microg Vs 531 ± 357,P=0.01). Significantly more patients in group A aborted within 24h and 48h {64(79%) and 79(97.5%) Vs 50(61.7%) and 72(88.9%), P=0.016 and 0.029 respectively}.

Only 2 (2.5%) patients in group A and 4 (4.9%) in group B failed to abort in 48h period, which is not statistically significant (*P*=0.66).

Although the complete abortion was higher in group B, the differences didn't reach statistical significance (Table 2). No complications were observed during surgical procedure (curettage) in either group.

Table 1. Baseline characteristics of study subjects.

	Group A(n=81) misoprostol 400	**Group B(n=81) misoprostol 200**	**P**
Age* (years)	27.2±5.6	27.7±5.9	0.6
GA* (weeks)	17.3	18.4	0.202
Gravidity **	2(1-7)	2(1-8)	0.145
Parity **	1(0-4)	1(0-4)	0.265
* mean ± SD	** median		

Table 2. Charecteristic of out come measure.

	Group A	**Group B**	**P**
Induction abortion interval*l(h)	14(10-22)	20 (12-30)	0.01
Total dose of misoprostol#(µg)	731± 362	531±357	0.001
Abortion rate within 24h	64(74%)	50(61.7%)	0.016
Abortion rate within 48h	79(97.5%)	72(88.4%)	0.029
Complete abortion	7(8.6%)	10(12.3%)	0.408
Incomplete abortion	72(88.9%)	67(82.7%)	0.0408
No response	2(2.5%)	4(4.9%)	0.66
* Median	#Mean ± SD		

Table 3. Adverse side effects

	Group A	**Group B**	**P**
Abdominal Pain	38(47%)	47(58%)	0.157
Nausea	5(6.2%)	3(3.7%)	0.468
Vomiting	13(16%)	5(6.2%)	0.046
Diarrhea	5(6.2%)	6(7.4%)	0.755
Fever	4(4.9%)	6(7.4%)	0.81
Overall	42(52%)	51(63%)	0.153

Adverse effects were common and similar between groups, and all were well tolerated (Table 3). In group A the overall incidence of side effects were 52%, being 63% in group B (*P*=0.153). The most common side effect was abdominal pain (47% in group A Vs 58% in group B, *P*=0.157). Vomiting was more common in group A (16% Vs 6.2%, *P*=0.046). In group A 33 (40.7%) patients required parenteral analgesics while in group B 43 (53.1%) had these requirements. (*P*=0.115) The hazard rate for abortion within 24h was found to be 1.6 fold greater in group A, once controlled for plausible confounders (OR=1.6, 95% CI:1.1-2.3, *P*=0.013, Cox regression).

DISCUSSION

Several studies have evaluated the use of misoprostol for induction of labor in the second trimester of gestation (3-12).Comparison among these studies is difficult because they included women with varying duration and different regimens. In this study we compared two regimens of 400µg and 200µg of misoprostol between14-24 week of pregnancy. The abortion rate within 24h was significantly more in 400µg group (79% Vs 61.7%). Dickinson et al reported similar results (76% Vs 59%)(3). The hazard rate for abortion within 24h was found to be 1.6 fold greater in group A. The abortion rate within 48h was also significantly more in 400µg group (97.5% vs 88.9%). Similar rates are reported by other authors(3,4). The induction-abortion interval was significantly less in 400µg (14h Vs 20 h) which was similar to Dickinson results (15h Vs 18 h)(3).

Although Jain et al reported induction-abortion interval of 13.8h and 14 h with 200 µg misoprostol every 6h and 12h(4). The mean amount of misoprostol administration in 400 µg group was significantly larger than in group 200 µg as was expected (731 µg ± 362 µg). Wong et al has reported misoprostol doses as 400 µg every 6 hour to be as high as 1546 µg ± 663 µg (11) which is much more than the dose used in our study. The need for curettage was high in our study and similar between groups (88.9% Vs 82.7%). Other studies have

reported a curettage rate from 8% to 66% (4,10). The lower rate of complete abortion in this study compared to other studies maybe due to waiting only 2h for placental expulsion. There was no difference in failure rate (fail to abort within 48h) between two groups(2.5 Vs 4.9%), but Dickinson reported a significant difference between this two regimens , 0% in 400 µg and 7.8% in 200 µg(3). Adverse effects were similar between groups and all were well tolerated (52% Vs 63%). Apart from abdominal pain the incidence of adverse effects was relatively low in both groups. Vomiting was seen significantly more in 400 µg (16% Vs 6.2%). Wong et al reported a 9% incidence of vomiting with median misoprostol doses of about 2000 and 1200 µg in two study groups(11). Diarrhea was similar between the two groups (6.2% Vs 7.4%). The incidence of diarrhea reported in vaginal administration of misoprostol vary from 0%(9,12), to 40% (13). Fever was seen in 4.9% Vs 7.4% of the two groups. Reported incidence of fever in previous studies of vaginal misoprostol are variable with values 12.2 % and 32.4% (11), 22%(7) and 50%(13).

In conclusion we have shown that 400 µg misoprostol every 6h is more effective than 200 µg misoprostol every 6h for the second trimester termination of pregnancy. The hazard rate for abortion within 24h was found to be 1.6 fold greater with 400 µg every 6h. The regimen with 400 µg misoprostol every 6h appears to be the preferred dose scheduled because of shorter induction abortion interval, more efficacy and similar adverse effect.

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