A Comparison between Dry and Moistened Intravaginal Misoprostol for Termination of Second Trimester Pregnancy: A Randomized Comparative Trial

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Abstract

Background: This study was conducted to evaluate the efficacy and safety of 200 µg misoprostol administered vaginally every 4 hours to a maximum of 48 hours for second trimester intrauterine fetal death.

Methods: We conducted a prospective, randomized trial comparing the efficacy and safety of misoprostol, a synthetic analogue of prostaglandin E1 "alprostadil", (200 µg intravaginally every 4 hours) either in its dry form (group A) or moistened with 1 ml of saline (group B). The study population included 136 pregnant women between 14 and 24 weeks' gestation who were seeking for termination of pregnancy because of intrauterine fetal death.

Setting: Woman’s Health Center, Assiut University.

Results: All patients in both groups aborted within 48 hours (100% success rate), the median induction-abortion interval was significantly shorter in group B than in group A (p<0.01) patients in group B had significantly short median induction-abortion interval (p<0.01), less total numbers of doses (p<0.05), less retained placenta (p<0.05), more abortion within 24 hours (p<0.01), more abortion with the 1st dose (p<0.01), but had more need for analgesia and more incidence of side effects (p<0.01).

Conclusions: The intravaginal administration of 200 µg of misoprostol tablet moistened with saline every 4 hours was effective for second trimester pregnancy termination and superior to dry misoprostol tablet. However, it was associated with more side effects which were well tolerated.

Key Words: Misoprostol – Second trimester pregnancy termination – Intrauterine fetal death.

Introduction

ABORTION-RELATED complications increase significantly as gestational age increases. Induction of abortion after 14 weeks of gestation is associated with a sharp rise in the rate of complications and in the consequent medical costs [1]. In addition, compared with women whose abortions were performed at or before 8 weeks of gestation, women whose abortions were performed in the second trimester were significantly more likely to die of abortion-related causes [2]. Various methods, including oxytocin infusion and amnioinfusion of hypertonic saline or urea, have been used previously for second trimester abortion and intrauterine death. There has been a recent worldwide trend towards alternative methods such as misoprostol use for second trimester abortion.

Misoprostol, a synthetic 15-deoxy-16-hydroxy-16-methyl analogue of naturally occurring prostaglandin E1 [3]. Although not registered for such use, misoprostol has been widely used in obstetrics and gynecology for cervical priming, medical abortion and induction of labour. Various doses, routes and protocols for medical termination of second trimester pregnancy have been investigated [4-6]. Intravaginal administration of drugs provides a slower, more constant rate of absorption than does oral ingestion [7]. Previous studies have demonstrated greater efficacy with vaginal misoprostol versus oral administration [8,9]. Nonetheless, drug absorption after vaginal administration varies widely and this may be due to the medium in which it is placed [10,11]. Therefore, a lot of institutions decided to administer misoprostol alone by the vaginal route to induce second-trimester abortion [12,13]. In previous studies, particulate remnants of misoprostol were identified at the time of repeat dosing [13,14]. Others have also revealed the incomplete dissolution of the tablets [15,16]. To overcome this problem, various investigators have used a tablet moistened either with normal saline [17-20] or with

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acetic acid [21-23] to increase its success rate, but they reported contradictory results.

Objectives:

The aim of our randomized trial was to compare the efficacy and side effects of 200 µg misoprostol tablet administered intravaginally every 4 hours either in dry form or moistened with 1ml saline for termination of second trimester intrauterine fetal death.

Materials and Methods

This prospective randomized trial was conducted from October 2007 through May 2008. One-hundred and thirty six healthy women requesting termination of second trimester pregnancy between 14 and 24 weeks, due to intrauterine fetal death, were recruited to the trial. After sonographic diagnosis of intrauterine fetal death and fulfilling inclusion criteria, patients were included into the study. Patients had to meet all of the following Criteria: {1} healthy women aged between 20 and 35 years old; {2} singleton dead fetus at 14-24 weeks' gestation; {3} no cervical dilation or effacement; {4} haemoglobin ≥10 mg/dl; {5} no active bleeding; {6} no history of rupture of membrane; {7} no known allergy to prostaglandins; {8} no previously scarred uterus; {9} not nursing mothers; {10} not using prescription drugs regularly; {11} not known pulmonary, hepatic, renal or cardiovascular disease. A written consent was obtained after they were informed that a pharmacological procedure would be taken to terminate pregnancy. They were also informed about the possible adverse effects and the possible use of other pharmacological or surgical methods if termination if failed to abort completely. The Research Ethics Committee of the Department of Obstetrics and Gynecology, Assiut University approved the study.

The women were randomly allocated to receive intravaginal 200 µg misoprostol tablet (Misotac 200 µg; Sigma PHARM. IND., S.A.E., Egypt) either in dry form in group A or moistened with 1 ml saline in group B. This was placed in the posterior fornix by a doctor at 4 hours interval and repeated if abortion had not occurred within a maximum period of 48 hours. The randomization schedule and envelopes bearing the subject number and allocation of grouping were prepared as described elsewhere [24]. The schedule was constructed so that the number in each group would be balanced for every 10 women recruited. The group assignments were put into sealed envelopes. The envelopes were opened when the women were recruited.

Before start of therapy, a blood sample was taken to determine haemoglobin, blood group and Rh factor. The adverse effects of misoprostol were recorded such as fever, pain, vomiting, chills and diarrhea were recorded every 4 hours. Antiemetics were given for nausea and vomiting and Pethidine hydrochloride 50 mg (Pethidine, MISR COM. FOR PHARM. IND. S.A.E, Cairo, Egypt) was given for pain relief, when indicated. The patients' vital signs were monitored every 2 hours and progression of abortion was assessed by cervical examination at the time of each drug administration. After abortion all patients received 20 IU of oxytocin in 1000 ml saline at an infusion rate of 125 ml/hour as in previous study [25]. Successful expulsion of products of gestation was determined by transvaginal ultrasound. Any retained products, if not expelled spontaneously within 1 hour after fetus expulsion, were removed with a sharp uterine curette under general anesthesia. A blood sample was taken after 12 hour of abortion for estimation of haemoglobin concentration.

The main outcome measures were: induction-abortion interval (time from placement of the first dose of misoprostol until the time of fetal expulsion); successful abortion (defined as expulsion within 48 hours); the total doses (how many tablets used for termination); the numbers of retained placentas; and decline in haemoglobin concentration. Secondary outcome measures were the side effects of the medication; including nausea, vomiting, diarrhea, chills and fever (temperature >38°C).

The estimation of sample size was based on the following assumptions: {1} a type I error of 10% and a type II error of 20% were acceptable because this trial was preliminary; {2} from a previous study, the successful abortion rate in 24 hours of women using misoprostol with a maximum of five doses was 80% [26]. In order to consider the regimen of vaginal misoprostol 200 µg every 4 hours as an acceptable method, the number of subjects in each group was 68.

The differences in the means of continuous variables were analyzed with the Student’s t-test for normally distributed data and with Mann–Whitney U-test for skewed data. Differences in proportions were analyzed with the 2 or Fisher’s exact test as appropriate.

Results

One-hundred thirty six women were enrolled in this study, 68 women in group A and 68 women in group B. All of the patients completed the study.
The distribution of patients' age, body mass index, parity and gestational age was similar in both groups.

Table (1): Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=68)</th>
<th>Group B (n=68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>27.3±3.5</td>
<td>29.1±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8±7.8</td>
<td>26.3±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>3.8±1.6</td>
<td>3.2±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>21.3±2.1</td>
<td>19.8±6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline haemoglobin (g/dl)</td>
<td>10.8±2.8</td>
<td>10.2±3.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group A received 200 μg misoprostol in dry form; group B received 200 μg misoprostol moistened with saline.

The characteristics of the abortion process and its relationship to the forms of misoprostol are shown in Table (2). The overall median (range) induction-abortion interval was significantly shorter in group B when compared with group A (5 "3-32" Vs. 9 "5-38" hours respectively; p<0.01). Number of misoprostol tablets was significantly fewer in group B than group A (1 " 1-4" Vs. 3 " 1-6" tablets, respectively; p<0.05). Abortion with the first dose of misoprostol was significantly higher in group B as compared with group A (39.7% Vs. 26.5%, respectively, p<0.01). The incidence of retained placenta was significantly higher in group A compared with group B (5.9% Vs. 1.5%, respectively; p<0.05). There was no statistically significant difference in mean haemoglobin between group A and group B (0.8 ±2.8 Vs. 0.6±3.3, respectively). None of the patients required further interventions to affect expulsion since all of them in both groups aborted within 48 hours. Considering analgesic requirements, more women in group B were in need for analgesia when compared to those in group A (55.9% Vs. 38.2% respectively; p<0.01).

Table (2): Comparison of outcome measures between groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=68)</th>
<th>Group B (n=68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction-abortion time (h)</td>
<td>9 (5-38)</td>
<td>5 (3-32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total number of doses</td>
<td>3 (1-6)</td>
<td>1 (1-4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Abortion within 24 h (n)</td>
<td>13 (19.1)</td>
<td>22 (32.4)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Abortion with first dose (n)</td>
<td>18 (26.5)</td>
<td>27 (39.7)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Retained placenta (n)</td>
<td>4 (5.9)</td>
<td>1 (1.5)</td>
<td>&lt;0.05**</td>
</tr>
<tr>
<td>Analgesic requirements (n)</td>
<td>26 (38.2)</td>
<td>38 (55.9)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Group A received 200 μg misoprostol in dry form; group B received 200 μg misoprostol moistened with saline.

1: Values are median (minimum-maximum ranges).
2: Values are given as number (%).
3: Mann-Whitney test.
*Fisher exact test.
**x² test.

The numbers of patients with and without side effects including nausea, vomiting, fever, chills and diarrhea are shown in Table (3). The incidence of side effects was significantly higher in group B than group A (82.4% Vs. 70.7%, respectively; p<0.01). The incidence of vomiting and fever, which were statistically significant, was more in women in group B than women in group A (13.2% Vs. 5.9% and 23.5% Vs. 10.3%, respectively; p<0.05). Also the incidence of nausea, chills and diarrhea was higher in women in group B than women in group A; however, the difference was not statistically significant.

Table (3): Incidence of side effects.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=68)</th>
<th>Group B (n=68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No side effects</td>
<td>20 (29.4)</td>
<td>12 (17.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (11.8)</td>
<td>11 (16.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (5.9)</td>
<td>9 (13.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fever</td>
<td>7 (10.3)</td>
<td>16 (23.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Chills</td>
<td>2 (2.9)</td>
<td>4 (5.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (8.8)</td>
<td>9 (13.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group A received 200 μg misoprostol in dry form; group B received 200 μg misoprostol moistened with saline.

Values are expressed as number (%). *: Fisher exact test.

Discussion

Misoprostol has been widely used for termination of second trimester intrauterine fetal death. Recent studies had been focused mainly on the optimization of misoprostol dosing regimen by comparing various dosages, dosing intervals and routes of administration [1]. Successful termination was generally considered to be the expulsion of the fetus within 48 hours. Misoprostol tablets are not prepared for vaginal use and local factors in the vaginal usage may play an important role in its efficacy. It is important to develop a preparation or medium that would ensure more complete dissolution of the vaginal misoprostol tablet in order to achieve optimal efficacy. The value of moistening misoprostol tablets administered intravaginally had been assessed by several studies. Some authors found that moistened misoprostol tablets were more effective for medical termination of pregnancy than dry tablets [17,19]. However, other authors concluded that tablet moistening before vaginal administration did not significantly improve efficacy [18,20].

This study showed that this regimen was effective, regardless of method used, in termination of pregnancy within 48 hours. However, regimen in group B was significantly more effective in achieving
termination with a short induction-abortion interval \(p<0.01\), in attaining abortion within 24 hours \(p<0.01\), and also in obtaining a higher abortion rate with the initial dose \(p<0.01\) than the group A regimen. Also, the total number of misoprostol tablets was significantly lower in group B than group A \(p<0.05\). The incidence of retained placenta was significantly higher in group A than group B \(p<0.05\). The need for analgesia was significantly higher in group B than group A \(p<0.01\). The incidence of side effects was significantly higher in group B than group A \(p<0.01\). The incidence of vomiting and fever were significantly higher in group B than group A \(p<0.05\). Also, the incidence of nausea, chills and diarrhea were higher in group B than group A, but the difference was not significant.

In our study, the overall success rate was 100% with median induction-abortion interval of 9 hours (5-38) in group A and 5 (3-32) in group B and the abortion rate within 24 hours was 19.1% in group A and 32.4% in group B. It had been reported that the successful abortion rate within 48 hours of a regimen of 400 \(\gamma\)g vaginal misoprostol every 6 hours in second trimester was 75.5%, the abortion within 24 hours was 60.8% and the mean induction-abortion interval was 43.4±6.4 hours \(p=0.01\). Other authors using misoprostol doses of 800 \(\gamma\)g every 12 hours for second trimester termination of pregnancy achieved a 91% complete abortion rate and 85.6% aborted within 24 hours \(p=0.01\).

The value of moistening misoprostol tablets administered intravaginally had been assessed by several studies. It was found that moistened misoprostol tablets were more effective for medical termination of pregnancy than dry tablets \(p<0.01\). In contrast, randomized multicentre trials revealed that tablet moistening before vaginal administration did not significantly improve efficacy \(p=0.01\).

In this study, the incidence of side effects in group A and group B were nausea (11.8% and 16.2%), vomiting (5.9% and 13.2%), fever (10.3% and 23.5%), chills (2.9% and 5.9%) and diarrhea (8.8% and 13.2%) respectively. In a study using 800 \(\gamma\)g misoprostol doses administered intravaginally at 12 hours interval to terminate pregnancy, the incidence of nausea 23.4%, vomiting 32.7%, diarrhea 54.3%, fever 21.9% and chills 77.7% \(p=0.01\). In a study using 400 \(\gamma\)g vaginal misoprostol every 6 hours for second trimester pregnancy termination, it showed that the frequencies were nausea 12.2%, vomiting 10.8%, fever 12.2% and diarrhea 2.7% \(p=0.01\). Another study, using 200 \(\gamma\)g misoprostol of moistened tablets intravaginally every 6 hours to terminate second trimester pregnancy, reported that the incidence were nausea 26.1%, vomiting 20%, diarrhea 21.5%, fever 27.6% and chills 38.5% \(p=0.01\). It was noticed that the longer the dose interval, the less the side effects \(p=0.01\).

Conclusion:

This study has shown that moistened misoprostol tablet at a dose of 200 \(\gamma\)g every 4 hours is very effective for second trimester medical abortion, due to intrauterine fetal demise, and is superior to dry misoprostol tablet. This regimen required less repeated doses and less time for pregnancy termination. However, it was associated with more side effects which were more or less well tolerated. Side-effects were mainly mild gastrointestinal and fever.

References

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