

## A comparison between two different doses of sublingual misoprostol in the management of first trimester incomplete miscarriage

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### Abstract

**Background and objective:** Various methods have been described for management of first trimester incomplete miscarriage. The active methods include surgical methods that are highly effective but are associated with anesthetics and surgical risks. Medical methods by Misoprostol had been shown to be effective, acceptable and widely used treatment for incomplete miscarriage. The aim of this study was to compare the efficacy, patients' acceptability and the side effects of sublingual administration of single dose of 400mcg with single dose of 600mcg of misoprostol in the treatment of first trimester incomplete miscarriage.

**Methods:** This study was conducted from April 1<sup>st</sup>, 2011 to February 1<sup>st</sup>, 2012 in the Maternity Teaching Hospital in Erbil city, Kurdistan region, Iraq. The study included 120 patients with incomplete miscarriage at a gestational age  $\leq 12$  weeks. They randomly received either single dose of 400mcg or 600mcg of misoprostol sublingually. Patients returned for follow-up and re-evaluation of abortion status after 7 days. Patients with a continuous incomplete miscarriage underwent surgical evacuation.

**Results:** The success rate in the first and second group was 90% and 91.7%, respectively, while patients' acceptability in the first and second group was 96.7% and 95%, respectively with no difference between both groups. Gastrointestinal side effects like nausea and diarrhea were more in the second group.

**Conclusion:** Single dose of 400 mcg of sublingual misoprostol is preferred on 600mcg of sublingual misoprostol regarding the development of side effects.

**Keywords:** Misoprostol, Incomplete miscarriage, Erbi City.

### Introduction

The term "miscarriage" is synonymous to spontaneous abortion and is often used with patients, because the word "abortion" is associated with elective termination.<sup>1</sup> Miscarriage or abortion is variably defined as the expulsion or extraction of a fetus (embryo) weighing less than 500 grams equivalent to approximately 20-22 weeks gestation or as termination before 24 weeks of gestation with no evidence of life.<sup>2</sup> Incomplete miscarriage is a type of miscarriage in which some, but not all of the products of conception have been passed. Retained products may be part of the fetus, placenta, or membranes. It can result from either spontaneous or induced

pregnancy loss.<sup>3</sup> Incomplete miscarriage continues to contribute to maternal morbidity and mortality in much of the developing world.<sup>4</sup> The complications which arise from incomplete miscarriage are hemorrhage and infection which occur because of remained tissue of conception or instrumentation through the cervix.<sup>2</sup> So safe and effective treatment for incomplete miscarriage is an important way to reduce abortion related morbidity and mortality.<sup>3,4</sup> Incomplete miscarriage can be treated with expectant management, or active management using medical or surgical methods.<sup>5</sup> Medical treatment of incomplete miscarriage has been categorized as a non- invasive option as it

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avoids the risks of women morbidity for those undergoing surgical evacuation, and require few resources and has the potential to improve greatly women's access to appropriate and effective care at secondary and even primary health care facilities. It is suitable for women far from surgical care facilities,<sup>6</sup> not wanting hospital admission or unfit for general anesthesia.<sup>5,6</sup> Misoprostol is a synthetic prostaglandin E1 analogue indicated for prevention and treatment of gastric and duodenal ulcers resulting from long-term use of non-steroidal anti-inflammatory drugs. It is available in tablets form 200 mcg and 100 mcg in the market since 1985 in more than 87 countries and can be administered by different routes; orally, vaginally, rectally, buccally and sublingually. It is cheap, easily available, can be stored at room temperature for up to three years without long term effects on the women's health.<sup>7</sup> In addition, misoprostol like natural prostaglandin affects more than one tissue of the body, including the stomach lining and the smooth muscle of uterus and the cervix.<sup>8</sup> Many studies have shown that the uterotonic and cervical ripening properties of misoprostol make it an accepted and widely used treatment for incomplete miscarriage.<sup>9</sup> The more recent studies suggest sublingual route of misoprostol to be the most potent<sup>10</sup>, and quickest onset of action compared to the other routes of administration due to high vascularity of buccal cavity. It also avoids the first pass effect through the liver,<sup>9,11</sup> and painful vaginal administration and is more convenient to be taken and acceptable by women.<sup>12</sup> The aim of this study was to compare the efficacy, patients' acceptability and the side effects of sublingual administration of single dose of 400mcg with single dose of 600mcg of misoprostol in the treatment of first trimester incomplete miscarriage.

## Methods

This comparative study was conducted from April 1<sup>st</sup>, 2011 to February 1<sup>st</sup>, 2012, at the Maternity Teaching Hospital in Erbil

city, Kurdistan region, Iraq. Among patients who attended the out-patient clinic, 120 pregnant women were interviewed and included in this study after taking written consent. All patients were cases of first trimester incomplete miscarriage with gestational age  $\leq 12$  weeks from last menstrual period. They had uneventful history with normal general examination. Gynecological examination revealed enlarged uterus with vaginal bleeding, and dilatation of the internal cervical os. Hemoglobin, blood group and Rhesus factor were estimated for patients under study. The diagnosis of incomplete miscarriage was confirmed by ultrasound examination showing evidence of retained products of conception. Exclusion criteria included signs and symptoms of hemodynamic instability or shock, suspicion of ectopic pregnancy, signs of pelvic infection and/or sepsis, known allergy to misoprostol or other prostaglandins, and history or evidence of disorders that represent contra-indication to the use of misoprostol like severe pulmonary diseases as asthma, congenital or acquired heart diseases, hypertension, prolonged use of corticosteroid, sickle cell anemia and adrenal insufficiency.<sup>12</sup> These patients were divided randomly into two groups (60 patients for each group). The first group received a single dose of 400 microgram misoprostol sublingually (Misotac). The second group received a single dose of 600 microgram misoprostol sublingually. These patients were instructed to hold these tablets under the tongue for about 30 minutes and after that any remaining tablet fragments can be swallowed with water.<sup>13</sup> Treatment success was defined as complete evacuation of the uterus without the need for surgical intervention. At the day 7 follow-up visits, the abortion status of each woman was assessed using clinical examination, including an interview, bimanual examination and ultrasound examination. Women with substantial retained products in the uterus on examination on study day 7 underwent surgical evacuation. When the treatment

was completed, women were interviewed to assess the acceptability of their assigned method. This study was approved by the Research Ethics Committee of the College of Medicine of Hawler Medical University. Written informed consents were obtained from all women accepted to participate in this study. The statistical package for the social sciences (version 18) was used for data entry and analysis. Chi square test of association and t-test were used whenever applicable. Chi square test of association was used to compare between proportions while t-test was used to compare between two means. A *P* value  $\leq 0.05$  was considered statistically significant.

### Results

The characteristics of both groups were compared regarding maternal age, parity, previous miscarriage and previous caesarean section are shown in Table 1.

The mean maternal age  $\pm$  SD of the first group was  $29.48 \pm 5.803$  years compared with the second group of  $28.93 \pm 5.301$  years ( $P = 0.589$ ). Eighteen patients (30%) in the first group and 9 patients (15%) in the second group had previous miscarriages, ( $P = 0.049$ ). In the first group 10 patients (16%) had previous caesarean section compared with 8 patients (13%) in the second group, ( $P = 0.16$ ). The distribution of gestational age in both study groups is shown in Table 2. The gestational age of 32 patients (53.3%) in the first group ranged between 5-8 weeks compared with 29 patients (48.3%) in the second group. The gestational age of 28 patients (46.7%) in first group ranged between 9-12 weeks compared with 31 patients (51.7%) in the second group. All these differences were statistically not significant.

**Table 1:** Demographic characteristics of patients in both study groups.

Variables	Group 1	Group 2	<i>P</i> value
Age in years (mean $\pm$ SD)	29.48 $\pm$ 5	28.93 $\pm$ 5.30	0.589
Previous miscarriages (No. & %)	18(30%)	9(15%)	0.049
Previous cesarean sections (No.&%)	10(16%)	8(13%)	0.16

**Table 2:** Distribution of gestational age in both study groups.

Gestational age	Group 1 No. (%)	Group2 No. (%)	Total No. (%)
5-8 weeks	32(53.3%)	29(48.3%)	61(50.8%)
9-12 weeks	28(46.7%)	31(51.7%)	59(49.2%)
Total	60(100%)	60(100%)	120(100%)

The outcome of medical treatment is shown in Table 3. Fifty four patients (90%) were successfully treated with single dose of 400mcg sublingual misoprostol compared with 55 patients (91.7%) were successfully treated with single dose of 600mcg sublingual misoprostol with no significant difference between the two groups. In the first group only six patients (10%) ended with surgical evacuation compared with only five patients (8.3%) in the second group with no significant difference between the two groups. Among these six patients (10%) in the first group, two patients (3.3%) developed severe vaginal bleeding in the first day of treatment and immediate evacuation was done by curettage compared with three patients (5%) in the second group. Another four patients (6.7%) in the first group were failed to complete miscarriage

during follow-up visit, and underwent surgical evacuation, compared with only two patients (3.3%) in the second group. Table 4 shows the frequency of side effects in the two groups. Most side effects were more common in the Group 2 compared with Group 1 with only nausea and diarrhea showing a statistically significant difference ( $P = 0.032$ ). The patients' acceptability in each study group is shown in Table 5. The acceptability rate in the first group was 58 patients (96.7%) compared to 57 patients (95%) in the second group ( $P = 0.85$ ), and the difference was statistically not significant. However, two patients (3.3%) in first group did not like to choose this method again in future if they were allowed to choose in comparison to three patients (5%) in the second group ( $P = 0.85$ ).

**Table 3:** The outcome of medical management in each of the study groups.

Outcome	Group 1 No. (%)	Group 2 No. (%)	P value
Success	54(90.5%)	55(91.7%)	0.752
Failure	6(10%)	5(8.3%)	
Total	60(100%)	60(100%)	

**Table 4:** Frequency of side effects occurred in both study groups.

Side effect	Group 1 No. (%)	Group 2 No. (%)	P value
Abdominal pain	19(31.7%)	26(43.3%)	0.187
Nausea	4(6.7%)	12(20%)	0.032
Vomiting	2(3.3%)	4(6.7%)	0.679
Diarrhea	4(6.7%)	12(20%)	0.032
Headache	4(6.7%)	7(11.7%)	0.343
Shivering	6(10%)	6(10%)	1.00

**Table 5:** Acceptability of patients in each study group.

Acceptability	Group1 No. (%)	Group No. (%)	Total	P value
Yes	58(96.7%)	57(95%)	115	0.85
No	2(3.3%)	3(5%)	5	
Total	60(100%)	60(100%)	120	

## Discussion

The World Health Organization estimates that maternal mortality from abortion-related complications accounts for 13% of all maternal deaths. Acute and long-term morbidities can include sepsis, hemorrhage and intra-abdominal injuries, while the resulting economic and emotional burden on families and communities is substantial.<sup>13,14</sup> Post-abortion care, a term commonly used by international reproductive health community refers to a specific set of services for women experiencing problems from all types of spontaneous or induced abortion.<sup>6</sup> Post-abortion care programs have recommended surgical methods for treatment of incomplete miscarriage, it works very well and provides a highly effective means of uterine evacuation, but surgical techniques require sterilized equipment along with providers skilled in their use and increased risks associated with anesthesia and instrumentation of the uterus.<sup>15</sup> Now post-abortion care programs recommended misoprostol for treatment of incomplete miscarriage since its safe, effective and acceptable nonsurgical method<sup>16,17</sup> based on the studies which documented the ability of misoprostol to induce uterine contractions and soften the cervix to empty the uterus in cases of incomplete abortion and miscarriage in the first trimester,<sup>15</sup> and use of misoprostol for medication-based post-abortion care services has the capacity to increase women's access to treatment of incomplete miscarriage and abortion and reduce the financial burden on the health-care system.<sup>18,19</sup> The results of this study were encouraging that sublingual administration of single dose of 400 mcg or 600 mcg misoprostol alone for medical evacuation of incomplete miscarriage up to 12 weeks successfully evacuated the uterus for 90% and 91.7% of patients respectively and acceptability was 96.7% and 95% respectively and there was no significant difference in both groups, and no serious adverse events were experienced by the

patients, and allows a significant proportion of women to avoid surgical intervention. No previous study was found to compare 400mcg versus 600mcg sublingual misoprostol and only few published studies using sublingual misoprostol in the treatment of first trimester incomplete miscarriage and abortion. A study by Diop et al compared the efficacy, safety and acceptability of single dose of 400 mcg sublingual misoprostol and single dose of 600 mcg oral misoprostol in 150 patients for management of first trimester incomplete miscarriage. They reported a high efficacy of single dose of 400 mcg sublingual misoprostol which was 91%, which is slightly higher than our result may be due to larger sample size, and acceptability rate was 97%.<sup>20</sup> Another comparable study done by Raghavan and Bynum included more than 200 women with first trimester incomplete miscarriage and they divided in to two groups, oral group received single dose of 600 mcg misoprostol and sublingual group received single dose of 400 mcg misoprostol. They found that sublingual group has same complete miscarriage rate compared with oral group with efficacy rate 90%, this finding matches with our result.<sup>21</sup> A study by Nevine et al from Egypt included 697 women with incomplete miscarriage and compared the safety, efficacy, and acceptability of single dose of 400 mcg sublingual misoprostol with that of manual vacuum aspiration. The result was high success rate in both study group, 98.3% for misoprostol group which is higher than our result and may be due to the larger sample size. Regarding the side effects, 4% of misoprostol group had vomiting, 33.9% had abdominal cramps and complications like heavy vaginal bleeding was reported in 3% of misoprostol users, and the acceptability was 97%. These findings matches with our results, but 40% of patients had nausea and 20% had chills which is higher than our results, which may be due to larger sample size.<sup>22</sup> This study agrees with a study done by Khadija et al



who compared the effectiveness of single dose of 600 mcg sublingual misoprostol with manual vacuum aspiration for treatment of incomplete miscarriage with a success rate of 92% and acceptability of 95%.<sup>23</sup> The frequency of side effects was similar to the findings of Sadia et al who conducted an observational study among 120 women to evaluate the role of single dose of 600 mcg sublingual misoprostol in the management of first trimester miscarriage. The diarrhea was observed in 20% of women, nausea in 19.2% and shivering was 5.6%, and the complications which reported in this study like heavy vaginal bleeding recorded in 4.7% of patients, and no infection was reported in this study which was similar to our results.<sup>24</sup> A comparable study done by Paritakul and Phupong that included 64 patients with first trimester incomplete miscarriage to compare single dose of 600 mcg sublingual misoprostol and single dose of 600 mcg oral misoprostol. These patients were evaluated at 48 hours after drug administration for complete miscarriage. The efficacy was high in both groups and the difference was statistically not significant. The acceptability rate of sublingual group reached up to 97%, which agrees with our study, but the success rate was 87.5% which was lower than our result. This may be due to their protocol which evaluated final study outcome after 48 hours or smaller sample size.<sup>25</sup>

### Conclusion

A single dose of 400 mcg sublingual misoprostol is preferred over a single dose of 600 mcg sublingual misoprostol, since it has similar efficacy of the latter in the treatment of first trimester incomplete miscarriage, with lesser gastrointestinal side effects and more acceptability by patients.

### Conflicts of interest

The authors report no conflicts of interest.

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