Original Article

Sublingual versus vaginal misoprostol in the management of missed miscarriage

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Abstract

Objective: To compare the efficacy of sublingual and vaginal misoprostol in the medical management of missed miscarriage.

Methods: Fifty women diagnosed as having missed miscarriage of gestational age less than 20 weeks were assigned randomly to receive 400µg of either sublingual or vaginal misoprostol every three hours, up to a maximum of five doses. The primary outcome measures were, complete evacuation of products of conception, mean induction to delivery time and the occurrence of side effects.

Results: There was no significant difference in complete evacuation rates between the sublingual misoprostol and the vaginal misoprostol groups (52% vs. 48%, p = 0.571) mainly within the first 24 hours. Mean induction to delivery time was also similar for both groups (13.07 ± 6.95 hours for sublingual versus 13.29 ± 5.63 hours for vaginal group) as was the total number of doses required (4.44 ± 1.04 for sublingual versus 4.52 ± 0.96 for vaginal misoprostol). Side effects were seen in 18 women (72%) in the sublingual group compared to 5 women (20%) in the vaginal group (p < 0.001). The incidence of unpleasant taste was significantly higher in the sublingual group than in the vaginal group (60% versus 4%, p = < 0.001).

Conclusion: Sublingual misoprostol is as effective as vaginal misoprostol for medical management of missed miscarriage but is associated with an increased risk of side effects especially an unpleasant taste (JPMA 60:113; 2010).

Introduction

Clinical miscarriage constitutes approximately 12% of pregnancies.[1] The standard treatment for missed miscarriage for the last 50 years has been dilatation and curettage which is typically done in an operating room, thus significantly increasing the costs.[2] Expectant and medical management of first trimester miscarriage possess significant economic advantages over traditional surgical management.[3] However there is uncertainty of timing associated with expectant management and the emotional trauma of carrying a non-viable pregnancy for a prolonged period may be stressful for some women.[4] Medical evacuation of missed abortion is an effective, safe and cost effective alternative to surgical evacuation of the uterus and is particularly suited to women not wanting hospital admission or a surgical procedure under general anaesthesia.[5] Medical management of missed abortion has been shown to reduce the need for D&C, is less costly and is associated with a high level of patient satisfaction.[6,7] Systemic bioavailability of vaginal misoprostol has been found to be three times higher than that after oral administration.[8] However several problems have been identified with vaginal misoprostol like inconsistent absorption which may be improved by dissolving the tablets in water and incomplete absorption of the tablet even after several hours of administration in addition to women finding vaginal administration uncomfortable.[9-11] More recent studies suggest sublingual route of misoprostol to be the most potent due to its highest bioavailability.[12]

This study was undertaken to compare the efficacy of 400 µg sublingual misoprostol with 400µg of vaginal misoprostol, in repeated doses, for medical management of missed miscarriage.

Patients and Methods

This was a prospective randomized open-labelled trial conducted in the Department of Obstetrics and Gynaecology Unit-III at Civil Hospital Karachi. A total of fifty women diagnosed as missed miscarriage were admitted in the ward from the out-patient clinic after doing a pelvic examination and taking an informed verbal consent. The inclusion criteria was an ultrasound diagnosis of missed miscarriage < 20 weeks gestation. Patients having incomplete miscarriage, retained products of conception (RPOCs) and previous caesarean section scars were excluded from the study. Women were randomized to sublingual or vaginal administration by opening consecutive sealed envelopes. Women in group 1 received 400 µg of misoprostol sublingually every three hours for a maximum of 5 doses and those in group 2 received 400 µg of misoprostol vaginally every three hours for a maximum of 5 doses. Patients having a gestational age of more than 12 weeks whose uterine size was also more than 12 weeks were given 200 µg of misoprostol instead of 400 µg in both sublingual and vaginal groups. Patients were monitored by the duty doctor for blood pressure, pulse, temperature, lower abdominal pain or

bleeding and for development of any side effects. Women were told to inform the duty doctor if they experienced any abdominal pain, vaginal bleeding, passed the gestational sac or developed any side effects like fever or shivering. Oral paracetamol two tablets were given if the woman complained of severe lower abdominal pain. Information regarding age, parity, gestational age, uterine size, ultrasound diagnosis, number of doses, induction to abortion interval, side effects and success or failure of treatment were recorded on structured proformas. Women who aborted the sac were sent for ultrasound pelvis to exclude any RPOCs. Those who failed to abort after receiving 5 doses of misoprostol and those who had incomplete miscarriage were taken for a surgical evacuation under general anaesthesia on the next day operation list and were discharged home 6 hours after the evacuation. Patients were not called for any follow up visit.

The primary outcome measures were, complete evacuation of products of conception, mean induction to delivery time and the occurrence of side effects. Acceptability of each method was assessed by verbally asking the patients whether they were satisfied with their treatment regimen, dissatisfied or neutral.

Results

The demographic characteristics of the women diagnosed with missed abortion are shown in Table-1. There was no significant difference with respect to age, parity, gestational age and uterine size between the two groups. The overall complete miscarriage rate was 50% (25/50 women). Fifty-two percent of women (13/25) in the sublingual group and forty-eight percent of women (12/25) in the vaginal group had a complete miscarriage. All patients who miscarried completely did so within 24 hours except one patient in the sublingual group who miscarried after 28 hours. Out of the 25 women in the sublingual group, 22 had a gestational age of 12 weeks or less and received 400 µg of sublingual misoprostol. Fifty percent (11/22) of these women had a complete miscarriage and 1 woman had an incomplete miscarriage. Two out of three women (66.6%), who had gestational ages of more than 12 weeks and were given 200 ug of sublingual misoprostol, had a complete miscarriage. Nineteen women in the vaginal group had gestational ages of 12 weeks or less and were given 400 µg of vaginal misoprostol. Ten of these women (52.6%) had a complete miscarriage. Six women whose gestational ages were more than 12 weeks were given 200 ug misoprostol vaginally. Two of these women (33.3%) had a complete miscarriage (Table-2). The mean interval between misoprostol administration and expulsion of products of conception was not significantly different between the two groups (13.07 ± 5.63 hours in the sublingual group vs. 13.29 ± 5.63 hours in the vaginal group). Eleven women (44%) in the sublingual group and thirteen women (52%) in the vaginal group failed to miscarry and had surgical evacuation. Table-3 shows the side effects of misoprostol in both groups. Side effects were significantly more frequent in the sublingual group compared to the vaginal group (72% vs. 20%, P=0.000). Unpleasant taste was the most frequent side effect of sublingual misoprostol seen in 60% cases against only 4% cases with vaginal misoprostol. Patient satisfaction was not significantly different between the two groups and closely followed the success rate of the regimen; 52% in the sublingual group and 48% in the vaginal group. Three women (12%) in the vaginal group said they were neutral.

Table-1: Demographic characteristics of women with miscarriages.

Demographic characteristics	Sublingual Misoprostol (n=25)	Vaginal Misoprostol (n=25)	p-value
Mean age in years	26.2 ± 4.17	26.4 ± 4.41	0.870
Parity; median (range)	2 (0-5)	2 (0-5)	0.845
Mean gestational age in weeks	10.08 ± 2.62	10.64 ± 2.92	0.480
Mean uterine size in weeks {range}	11.60 ± 2.08 {8-16}	11.64 ± 2.54 {8-18}	0.952

Table-2: Clinical outcome of medical management of missed miscarriage.

Clinical outcome	Sublingual Misoprostol (n=25)	Vaginal Misoprostol (n=25)	p-value
Complete miscarriage rate: n (%)	13 (52.0%)	12 (48.0%)	0.571
≤ 12 weeks: n (%)	11/22 (50.0%)	10/19 (52.6%)	0.557
> 12 weeks: n (%)	2/3 (66.6%)	2/6 (33.3%)	0.404
Mean induction to abortion interval in hours	13.07 ± 6.95	13.29 ± 5.63	0.931
Mean No. of doses required for complete miscarriage: {range}	4.44 ± 1.04 {1-5}	4.52 ± 0.96 {1-5}	0.779

Table-3: Side effects of treatment: Values are expressed as n (%).

Side Effects	Sublingual Misoprostol (n=25)	Vaginal Misoprostol (n=25)	p-value
Having side effects	18 (72%)	5 (20%)	<0.001
Nausea	5 (20%)	1 (4%)	0.094
Unpleasant taste	15 (60%)	1 (4%)	<0.001
Shivering	6 (24%)	4(16%)	0.362

Discussion

To the best of our knowledge this is the first study from Pakistan to compare the sublingual misoprostol with vaginal misoprostol in the management of missed miscarriage. The overall success rate for complete miscarriage in the first

trimester was 50 % which is comparable to a study from Lahore which reported a success rate of 53.1% with oral misoprostol 400 µg initially followed by 200 µg every 4 hours (4 doses).[13] However it is much less compared to that reported by similar studies from China and India which used 600 µg of sublingual and vaginal misoprostol and reported an overall success rate of 87.5% and 86% respectively.[14,15] This higher success rate may be related to the higher dose (600 µg) of misoprostol used in those studies. In addition the low success rate of our study could also be due to early evacuation performed after the failure of the five doses to achieve complete miscarriage, since we did not advise our patients to wait or to repeat therapy as done in some other studies.[4,14-16] It has been recommended that a waiting period of 7 days should be allowed to maximize the chances of success and to reduce the number of unnecessary surgical evacuations.[14]

There was no statistically significant difference in the complete miscarriage rates of first trimester missed miscarriages between the sublingual and vaginal groups. Similar findings have been reported by the above mentioned study from China.[14] Similarly our study showed no significant difference in the complete miscarriage rates between the two groups in the second trimester missed miscarriages although the sample size of second trimester miscarriages was very small. A study which compared the efficacy of sublingual and vaginal misoprostol in second trimester termination of pregnancy has reported a higher success rate (85%) for vaginal misoprostol compared to sublingual misoprostol (64%) at 24 hours but there was no significant difference in the abortion rate at 48 hours.[17] According to the Systematic Review of the Cochrane database, sublingual misoprostol is as effective as vaginal misoprostol in causing complete miscarriage but is associated with more frequent diarrhea.[18]

The induction to abortion interval was slightly shorter in the sublingual group than the vaginal group but the difference was not statistically significant. The number of women who aborted within 12 hours was 57% in the sublingual group compared to 41.6% in the vaginal group. This may be explained by the quicker and higher peak serum concentrations of sublingual misoprostol compared to the vaginal route.[12]

The incidence of side effects was three times more in the sublingual group than in the vaginal group, the most common being an unpleasant taste. A study from UK which compared sublingual and vaginal misoprostol for medical abortion also reported unpleasant taste in 63.9% of women in the sublingual group as compared to 37.5% of women in the vaginal group ($p = 0.02$).[19] In addition, two other studies comparing sublingual and vaginal misoprostol have reported a significantly increased frequency of unpleasant taste in women taking sublingual misoprostol.[20,21] It is suggested that this side effect may be overcome by making the misoprostol tablet sugar coated. Other side effects like nausea and shivering were also seen slightly more frequently in the sublingual group. This increased frequency of side effects may be explained by the higher bioavailability of sublingual misoprostol.[12]

Assessment of patient satisfaction was limited in our study as being an open label study, patients already knew the route of administration they were assigned to and the treatment outcome may have affected their preference. Another major limitation of our study was its small sample size. However, this study can serve as a pilot study for a future large randomized double blind clinical trial to compare the efficacy of sublingual versus vaginal misoprostol in the management of missed miscarriage.

Conclusion

Sublingual and vaginal misoprostol are both equally effective for the medical management of missed miscarriage although their overall effectiveness is low within the first 24 hours. Sublingual misoprostol is associated with more side effects especially an unpleasant taste.

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