

Sublingual misoprostol in the management of first trimester miscarriage

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Abstract

Objective: To evaluate the role sublingual misoprostol in the management of first trimester miscarriage.

Materials & Methods: This is an observational study .Hundred twenty women with diagnosis of missed or incomplete miscarriage less than 13 weeks were recruited. Two doses of 600ug of misoprostol sublingually 3hour apart for missed miscarriage and single dose of 600ug sublingually for incomplete miscarriage was given and left to work for 7-14 days. Women with fever, haemoglobin less than 9 g/dl, heavy vaginal bleeding requiring emergency surgical evacuation , contraindication to prostaglandin therapy were excluded from study. Primary outcome measures were complete evacuation of products of conception, mean induction to delivery time , occurrence of side effects and acceptability .The data was entered and analyzed on SPSS version 13.

Results: The efficacy of sublingual misoprostol in our study is 95%. 55% achieved complete evacuation of uterus in first 24hrs whereas 33% achieved it in 48 hours. There were minimal side effects with no major complication seen. Diarrhea was observed by 20% women whereas 15% complained of unpleasant taste. 2-5% had nausea and shivering. Patient satisfaction was 97% and acceptability 95%.

Conclusion: Misoprostol promises to have an important public health impact. Women and health care system worldwide could significantly benefit from this non-invasive treatment option. In low resource countries where infection, hemorrhage and uterine damage are far too commonly reported as consequences of poor surgical care , misoprostol treatment can prove to be a tremendous step towards reducing morbidity and mortality due to abortion complications worldwide.

Keywords: Sublingual misoprostol, missed abortion, miscarriage

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Introduction:

First trimester miscarriage is one of the most common complications of pregnancy occurring in 10-15% of clinically recognized pregnancies¹ South-Asia (Bangladesh, Nepal, India, Pakistan and Sri-lanka) being highly populated, resource constrained and underdeveloped region, holds almost one third (30%) of world's maternal deaths and approx 13% of them are related to abortions and its procedures² In Pakistan, approximately 890,000women present with missed abortion or incomplete abortion annu-

ally whereas annual abortion rate is 29 per 1000 women aged 15-49 years³.

Dilatation and evacuation of uterus has been the standard, commonly accepted approach to early pregnancy failure over a period of 50 years with more than 95% success rate⁴. The complications (haemorrhage and sepsis) associated with the procedure when done by unskilled personal commonly in low resource countries has changed the focus towards expectant and medical management with significant economic ad-

vantage as well⁵. Expectant management is an option for incomplete spontaneous abortion but the sub-optimal success rate (25-76%)^{6,7}, unpredictable interval to spontaneous expulsion, the uncertainty and anxiety, along with emotional trauma carrying non-viable pregnancy often makes expectant management less appealing to patients.

Medical management of early pregnancy failure is an effective, safe and cost effective alternative to surgical method and suitable for women not wanting hospital admission or unfit for general anesthesia⁸. Misoprostol, prostaglandin E1 analogue, is a safe option and gaining popularity because of its uterotonic and cervical priming action. It is inexpensive and stable at room temperature. A pharmacokinetic study compared oral, vaginal, sublingual and rectal routes of administration of misoprostol⁹. Sublingual route avoids first pass effect through the liver, has the shortest time to peak concentration that is 30 minutes as compared to 75 minutes in vaginal route and greatest bioavailability as compared to other routes, due to high vascularity of buccal mucosa. It also avoids painful vaginal administration and is more convenient to take and acceptable by women.^{10,11,12} The main drawback is gastrointestinal side effects, shivering and hyperthermia.¹² Almost twenty different studies have evaluated efficacy of misoprostol in early pregnancy failure with success rate ranging from 13-100% which is influenced by many factors as diagnosis, sac size, and number of doses. Two recent trials documented efficacy rates above 90% when compared to manual vacuum aspirator.^{13,14}

There are multiple dosage regimes available in literature given through different routes for first trimester failures with only few using sublingual route. Limited data on sublingual route as compared to other routes has motivated us to design this study. The rationale of performing this study was to evaluate the efficacy, acceptability and dose of misoprostol when given sublingually in the management of first trimester pregnancy failure.

Materials and methods:

This is an observational study conducted in out patient clinics of Hamdard University hospital. A total of 120 patients with the diagnosis of missed and incomplete miscarriage upto 13 weeks were invited to participate into the study after taking informed consent. They were given choice of selecting either surgical or medical method of management. Those who opted for outpatient medical therapy were included.

Diagnosis of missed miscarriage was made when os was closed, nil or mild vaginal bleeding, anembryonic or no fetal cardiac activity seen on ultrasound. Incomplete miscarriage was diagnosed when there was history of passage of tissue and/or blood, os was open mild or moderate bleeding or an ultrasound showing fetal remnants. Complete miscarriage was diagnosed on ultrasound showing empty uterus with no evidence of retained products of conception.

Women with fever, haemoglobin less than 9 g/dl, heavy vaginal bleeding requiring emergency surgical evacuation, contraindication to prostaglandin therapy (asthma, hypertension, glaucoma, mitral stenosis) were excluded from study.

All eligible women who consented were counseled and given detailed information about the protocol. For incomplete abortion single dose of 600ug was given sublingually. For missed miscarriage, 600ug of misoprostol was given sublingually and repeated after 3 hours – 2 doses only, and were sent home to wait for 7-14 days until complete miscarriage. The patients were explained about side effects and were instructed to report if they have shivering, diarrhea, nausea/vomiting, excessive cramping or unbearable pain or heavy bleeding. They were told that bleeding may start anytime and complete abortion may take one to two weeks. In case of profuse bleeding explained as soaking more than 2 extra large sanitary pads an hour for more than 2 consecutive hours, or bleeding continuously for 2 weeks they were instructed to report back to hospital. For pain management tab paracetamol was prescribed.

Once the women reports back with history of passage of tissue and /or blood at home ultrasound was done in all cases to confirm complete miscarriage. In case of retained products of conception third dose of 600ug is repeated sublingually and left to work for a total of 14 days from the first dose. All women were followed up till complete abortion or 14 days. Patients who refused to wait for long time and were unsatisfied were admitted and surgical evacuation was performed. The primary outcome measures were complete evacuation of products of conception, mean induction to delivery time, occurrence of side effects. Acceptability was assessed by verbally asking the patients if they were satisfied with their treatment or unsatisfied. Data was entered and analyzed in SPSS, version 13.

Results:

A total of 120 patients with missed miscarriage (100 women) and incomplete miscarriage (20 women) upto 13 weeks of gestation were included in the study. The mean age of patients was 26.2 + 4.17. Majority of women were multiparous, median parity was 3, range (0-6). Mean gestational age 10.0 + 2.5 weeks. Table 1.

Complete evacuation of uterus was achieved in 114 women, remaining six underwent surgical evacuation of uterus thus the efficacy of sublingual misoprostol in our study is 95%. Table 2. Out of 114 women 110 had complete miscarriage by the end of 7 days with 2 doses of 600ug sublingual misoprostol – 3 hours apart. four patients were given third dose of 600 ug sublingual misoprostol as they came with retained products of conception at 7th day. Single dose of misoprostol was given to all incomplete miscarriage and all of them had complete miscarriage in first 24 hrs. Total six women underwent surgical evacuation 2 due to heavy bleeding and remaining 4 were unsatisfied and could not wait longer. Efficacy of sublingual misoprostol is 55% in 24 hours of administration of drug and 33% in 48 hrs, although majority of our patients were from missed miscarriage. table 1. Only 3 % required third dose after waiting till 7 days and then had complete miscarriage within 24 hours of its administration. A total of 6 women had

Table 1: Demographic characteristics of women with miscarriages

Demographic characteristics	N= 120
Mean age in years	26.0 + 4.1
Parity median (range)	3 (0-6)
Mean gestational age in weeks	10.0 + 2.6
Previous cesarean section	26
Diagnosed as missed miscarriage	100
Diagnosed as incomplete miscarriage	20

+ Standard deviation

Table 2: Outcome measures

	Number (%)
Induction to delivery time	
24 hrs	66 (55%)
48hrs	40 (33.3%)
72hrs	9 (7.5%)
96hrs	1 (0.8%)
7days	4 (3.3%)
Treatment doses	
One dose	20 (16%)
Two doses	96 (80%)
Three doses	4 (3.3%)
Blood loss	
Mild	24 (20%)
Moderate	90 (75%)
Heavy	6 (5%)
Side effects	
Shivering	6 (5%)
Nausea	3 (2%)
Unpleasant taste	19 (15%)
Diarrhea	24 (20%)
Satisfaction	
Satisfied	116 (97%)
Unsatisfied	4 (3%)
Acceptability	
Yes	114 (95%)
No	6 (5%)

heavy bleeding remaining had mild to moderate.

We also included women with history of previous cesarean sections in our study. We had 16 patients with previous one cesarean section and 10 patients with previous 2 cesarean sections who were given same dose of misoprostol as others with no added complications.

Regarding side effects only 20% observed Diarrhea, 5% shivering, 2% nausea, 15% unpleasant taste. Patient satisfaction was 97% (116) only 4 women were unsatisfied who refused to wait longer for spontaneous complete miscarriage and opted for surgical evacuation on 3rd day of treatment. Acceptability was 95% whereas 5% does not like to choose method again.

Discussion:

This study demonstrates the efficacy and safety of out patient medical management of first trimester miscarriage. The use of two doses of 600ug misoprostol sublingually with follow up for 7-14 days reduced the need of surgical evacuation by 95%. In addition this dose and route achieved 55% complete miscarriage in first 24 hrs and remaining 33% is achieved in 48 hours following therapy. We also found that women with spontaneous incomplete miscarriage were more likely to have complete expulsion after one dose of 600ug sublingually than women with missed miscarriage. The higher patient satisfaction in our study also reflects successful outcome which highlights the importance of counseling women before opting for medical management regarding side effects, waiting time of 7-14 days and the need for surgical intervention in those who fail to successfully evacuate the uterus within this time frame.

The overall success rate for complete miscarriage in our study is 95% which is comparable to similar studies reported from China and India. They used 600ug of sublingual and vaginal misoprostol and reported an overall success rate of 87.5% and 86% respectively^{15,16} whereas khadija et al¹⁷ from pakistan reported 92% success after single dose of sublingual misoprostol. The higher success rate in our study may be due to waiting time of 7-14 days as it is well recommended that waiting period of 7 days should be allowed to maximize the chances of success and to reduce the number of unnecessary surgical interventions.¹⁵ Two studies comparing a single dose of oral misoprostol 600ug versus 600ugx2 doses (with a 4 hour interval) showed no difference in efficacy between the two regimen.^{18,19} Weeks et al used 600ug of oral misoprostol and

showed success rate of 96.3%.¹⁹

Different misoprostol alone regimen have been reported in literature for medical management of first trimester miscarriage. These studies are difficult to compare as different regimens and waiting time was used. WHO clinical guidelines 2007 clearly recommends 600ug of sublingual misoprostol only 2 doses 3 hours apart for the management of first trimester missed miscarriage with waiting period of 7-14 days.²⁰ We also used the same regime in our study which finished in 3 hours time and have the advantage of sending patient back to home, efficacy of 95%, cost effective, safe and acceptable.

Sublingual and oral route of administration has reported higher incidence of side effects in literature. We found 5% of our patients reporting shivering 2% nausea, 20% diarrhea and 15% unpleasant taste. Similar rates of diarrhea, 21% are reported by J.S Bagratee²¹ from south Africa whereas Tang et al¹⁵ found 70% incidence of diarrhea in their study. The unpleasant taste in our study was only 15% while a study from UK reported 63%.²² Blood loss as reported by patients in our study was moderate in 75% of cases, heavy loss was observed in only 6 cases, 2 of them were hospitalized and underwent surgical evacuation, remaining 20% had mild bleeding, again reflecting the safety of misoprostol. It appears that our regimen of 600ug sublingual upto two doses was well tolerated by our patients with not much increase in side effects, pain or bleeding.

The introduction of any new management intervention must also convince health providers that in addition to safety and tolerability, it must be acceptable to patients. We have found that our medical regimen is associated with high degree satisfaction and acceptability. Woods and Grazio et al^{23,24} also found high satisfaction in their study on medical management. It is attributed to low cost involved, advantage of being at home, less chance of hospitalization, out patient procedure with no anesthesia involvement, easy to take with tolerable side effects. Counseling plays a vital role before undertaking treatment. We counsel the women well about time period

involved, side effects, pain, amount of bleeding expected and when & where to report in case of need, so is the reason that most of them remained satisfied.

Abortion related complications contributes greatly towards maternal mortality in South Asia including Pakistan. Medical management using misoprostol could revolutionize the existing treatment options of abortions. This method greatly improves access to services by enabling women to seek effective, appropriate care at secondary and even primary health care facilities, with non surgically trained, mid-level providers. It would decrease the burden on tertiary health care facilities and economic resources because of its low cost, as well as reducing the need for surgical supplies, sterilization and anesthesia. Through this study we also prove the additional benefit of efficacy, safety, and acceptability of misoprostol in first trimester miscarriage.

Conclusion:

Misoprostol promises to have an important public health impact. Women and health care system worldwide could significantly benefit from this non-invasive treatment option. In low resource countries where infection, hemorrhage and uterine damage are far too commonly reported as consequences of poor surgical care, misoprostol treatment can prove to be a tremendous step towards reducing morbidity and mortality due to abortion complications worldwide.

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