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Original Article

Oral Versus Vaginal Misoprostol in the Management of Missed Abortion

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Abstract

Missed abortions are common and represent a significant gynaecological emergency workload. The search for a non invasive method with high success rate has led to the use of misoprostol. Most research into the use of misoprostol for the medical evacuation of missed abortion has concentrated on its effect after oral administration. Recent evidence suggested an improved efficacy of uterine evacuation and a reduced incidence of side-effects if misoprostol was administered vaginally. The present study has been designed to compare the safety and efficacy of oral versus vaginal misoprostol for medical management of missed abortion.

The present study was experimental and randomized. A total of 100 women with pregnancies of < 12 weeks from last menses (verified by ultrasound) were recruited for the study. Eligible women were allocated randomly to the two treatment groups by means of lottery. The primary outcome was measured by complete expulsion rate. The secondary outcome measure was patient's side effects and satisfaction. The following variables were compared: complete or incomplete expulsion of the conceptus in 24 hours, induction expulsion interval time, side effects; dilatation of cervical canal in those patients who required surgical intervention, number of doses required, women's perception and duration of hospital stay.

The present study demonstrated that early expulsion of the product following induction, complete expulsion of the product after 24 hours, were significantly higher in the vaginal misoprostol group than those in the oral misoprostol group. The dose of misoprostol was also much lower in the vaginal group compared to the oral group. The need for surgical evacuation was markedly decreased in the vaginal group than that in the oral group.

So, treatment of missed abortion by misoprostol through vaginal route should be explored for introduction into health care delivery system nation wide.

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Introduction

Missed abortion is a significant gynaecological emergency both in highly sophisticated societies and in less developed communities. It refers to the clinical situation in which interruption of the pregnancy occurs before the age of viability where the embryo/foetus is retained inside the uterine cavity for a variable period of time[1].

The most common complication of pregnancy is spontaneous abortion. Spontaneous abortion occurs in about 14–19% of clinical pregnancies. Missed abortion contributes a considerable figure to this percentage [2].

Most pregnancy losses occur in the early weeks rather than at any other gestational age. Approximately 50% of spontaneous abortions occur during the first trimester. This incidence decreases to 20-30% in second trimester losses, & 5-10% in third trimester losses[3]. The aetiology of spontaneous

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abortion is often complex & obscure. However, majority (50%) of early abortions are due to chromosomal abnormality in the conceptus.

In Bangladesh, approximately half the admissions in gynaecological units of major urban hospitals are for complications of abortion. In 2004 abortions related deaths were found to be nearly 21% in Bangladesh. In another study, it was seen that mortality due to abortion accounted for one third of the pregnancy related deaths. Not only mortality, various complications of abortion may also lead to long term morbidities[4].

A portion of these abortions diagnosed as missed abortion, presents with mild symptoms like those of threatened abortion followed by absence of usual signs of progress of pregnancy. Sometimes there may be no bleeding and the condition is diagnosed clinically when the doctor notices that the uterus is not increasing in size. The uterus may be found smaller than would be expected and on ultrasonographic scan will reveal the true state of affairs[5].

Sonographic signs suggestive of a nonviable pregnancy include - irregular gestational sac, nonliving embryo (embryo without a heart beat) and presence of abnormal hyperechoic material within the uterine cavity[6].

The standard management of spontaneous abortion up to the 1990s was the universal evacuation of the retained products of conception, and this management had been undertaken for the preceding 60-70 years.

The procedure has a remarkable impact on health budget. In the US, it was estimated in 1998 that 100,000 uterine curettages were performed annually for early pregnancy failure at a yearly cost of over $100 million[7]. The overall complication rates with surgical evacuation are between 4 and 10%, and consist of excessive bleeding, uterine perforation, pelvic infection and cervical injury. Uterine synechia, infertility and adenomyosis may occur in long term[8].

By the 1990s, people were beginning to question whether such an invasive method was really necessary to evacuate the uterus in missed abortions[7].

An alternative approach to surgical management is expectant management, which is waiting for the process of pregnancy loss to end spontaneously without any intervention. The success rate with this approach for early pregnancy failure ranges from 25-75%. With this method, the time to spontaneous expulsion is unpredictable and can be up to a month. For patients, this method creates uncertainty, anxiety, sadness resulting from pregnancy loss, and sometimes coagulation defects may appear and some women may still need surgery. So this management approach is often not appealing[9].

So alternative treatment approaches have come up. For this Prostaglandins and their synthetic analogues are successfully employed in the medical management of missed abortions. There is continual search for better agents, routes of administration and doses of prostaglandins for medical termination of pregnancy. Investigations to date mainly focused on the use of synthetic prostaglandin analogue, misoprostol[10].

There is a plethora of different combinations of medical treatment regimens for the management of missed abortion. Most research into the use of misoprostol for the medical evacuation of missed abortion has concentrated on its effect after oral administration. Recent evidence suggested that there might be an improved efficacy if misoprostol was administered vaginally[11,12].

When Misoprostol tablets are placed in the posterior fornix of the vagina, plasma concentrations of Misoprostol acid peak in one to two hours and then decline slowly. Vaginal application of Misoprostol results in slower increases and lower peak plasma concentrations of Misoprostol acid than when administrated orally, but overall exposure to the drug is increased[13,14].

Investigations into the absorption kinetics and uterine activity also suggested that vaginal administration should be more effective in uterine evacuation and at the same time, had less systemic side effects compared with oral administration [15,16].

This prospective randomized clinical trial evaluated the efficacy, side-effects, need for surgical evacuation & short term complications associated with oral & vaginal administration of misoprostol. Thereby the study compared the safety and efficacy of oral versus vaginal Misoprostol for medical management of first trimester missed abortion.

Material and Methods

This interventional and randomized control trial study was conducted in the Department of Obstetrics & Gynaecology of Rajshahi Medical college Hospital from July,2011 to June 2012.Patients admitted during the study period with clinical features of abortion were taken as study population. Haemodynamically unstable patients, patients with septic abortion, known allergy to misoprostol or associated serious co-morbidities were excluded. A total of 100 women with pregnancies of < 12 weeks from last menses (verified by ultrasound) were recruited for the study as sample. Neither the investigator nor the women was blinded to the treatment assignment.

Before admission to the study, potential subjects undergone ultrasound examination to verify the length of the pregnancy and check that the pregnancy is intrauterine. Full medical and gynaecological examinations including pelvic examination were performed as a routine. Haemoglobin measurement; the blood group and Rh typing were also performed. A woman who fulfilled the criteria for admission and who were willing and able to participate in the trial and had given their informed consent was included in the study.

Eligible women were allocated randomly to the two treatment groups by means of lottery. In group "O" 400ug of misoprostol was given orally and repeated every four hours for maximum of three doses. In group "V" 400ug of misoprostol was inserted into the posterior fornix of vagina and then the patients remained in a semi prone position for at least 1 hour. Dose was repeated every four hours, for a maximum of three doses. 4 hours after initial dose, the patients were evaluated by pelvic examination. If after initial dose, complete abortion had not occurred; the second equal dose was placed. This was followed in both groups.

After three doses of misoprostol; over the next 12 hours; complete, incomplete or no expulsion were documented clinically and sonographically.

Absence of echogenic structures was suggested as complete abortion.

Success was defined as a complete uterine evacuation without the need for surgical intervention within 24 hours.The treatment failure was defined as no evidence of complete abortion within 24 hours.

Results

The clinical outcome in current study shows that Complete expulsion occurred in 44 (88%) of the patients in vaginal group and 25 (50%) of the patients in oral group as revealed by ultrasonography after 24hours of initiation of therapy which was highly significant statistically.

Table I. Rate of complete expulsion in 24hours.

Completeness of expulsion in 24 hours	Group		p-value
	Oral (n =50	Vaginal (n = 50)	
Complete expulsion	25(50%)	44(88%)	<0.001
Incomplete expulsion	25(50%)	6(12%)	

Per vaginal excessive bleeding as a measure of primary safety end point revealed that Only 2 (04%) patients in Oral group and 01 (02%) patient in vaginal group developed excessive bleeding, this was not significant.

Interval between induction & expulsion has an important bearing on acceptability. In the present study the mean time interval of expulsion in group V was 8.2 hours with SD of ± 2.9 ; while in group O it was 17.2 hours with SD of± 3.1. This difference was highly significant.

Table II. Comparison of induction and expulsion interval time in hours.

Time in hours	Group		p-value
	Oral (n =50)	Vaginal (n = 50)	
	17.2 ± 3.1	8.2 ± 2.9	**0.006**

The different doses that were needed for initiating expulsion of the product of conception in two

groups were found to be highly significant. No patient in oral misoprostol group expelled after single dose but 28% patients in vaginal misoprostol group expelled after single dose. While 34% patients in oral misoprostol group and 50% patients in vaginal misoprostol group expelled after second dose. Most (66%), of the patients in oral group required third dose for expulsion but only 22% patients in vaginal group required third dose.

The need for surgical evacuation was staggeringly decreased in the vaginal group than that in the oral group..Surgical intervention (D&C) was performed in the following cases:

1) Incomplete expulsion in 24 hours: 6 patients in vaginal misoprostol group and 25 patients in oral misoprostol group.

2) Excessive vaginal bleeding: 1 patient in vaginal misoprostol group and 2 patients in oral misoprostol group developed excessive bleeding. All of them had incomplete expulsion.

Table III comparison of rate of surgical intervention (D&C) required in two groups

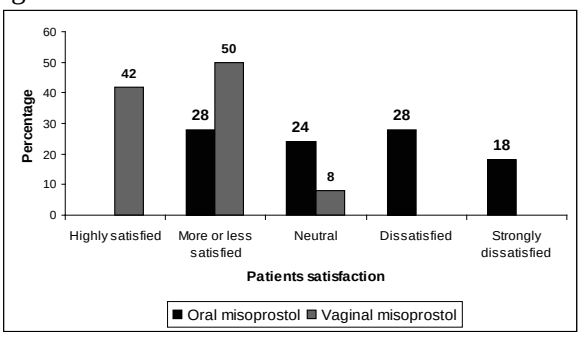
Number of Surgical evacuation	Group		p-value
	Oral (n =50)	Vaginal (n = 50)	
	25(50%)	6(12%)	<0.001

One of the aims in present study was to assess cervical permeability in patients who required surgical evacuation. A change in route of administration from systemic to local has resulted in marked softening effect in cervix.83.3% patients in vaginal misoprostol group and 52% patients in oral misoprostol group had well dilated cervix as found during Dilatation and curettage. A good permeability was defined as the ability to pass a No. 8 Hegar dilator.

Majority (84%) of the patients in Oral misoprostol had to stay in the hospital for 5–9 days, while majority (76%) of the patients in the vaginal misoprostol group had to stay for the same duration. The mean hospital stay was significantly less in the vaginal misoprostol group (4.4 ± 1.9 days) than that in the oral misoprostol group (5.6 ± 1.6 days) (p = 0.001).

Oral misoprostol group encountered a higher frequency of non serious adverse events like nausea, vomiting, fever and diarrhoea compared to their vaginal counterpart (p = 0.031, p = 0.023, p = 0.500, p = 0.181 and p = 0.500 respectively). However, muscle cramping demonstrated significantly present in the vaginal group compared to the oral group (p = 0.028).

Patient's satisfaction was assessed by asking the subjects to rate their degree of agreement with two statements: 1) I would recommend the treatment with the vaginal tablets/oral tablets to a friend or family member who had a missed abortion. 2) I would try treatment with the vaginal/oral tablets again if I had another missed abortion.



Discussion

Early pregnancy failure occurs in 15% of clinically recognized pregnancies. Approximately one in four women will have an early pregnancy failure during her lifetime. For most of the 20th century, dilatation and curettage was the commonly accepted approach to early pregnancy failure. This practice can be traced back to the late 19th and early 20th century. In more recent years, the medical community began to question whether evacuation by surgical intervention was necessary for uncomplicated cases of early pregnancy failure[16].

The results of this study document the safety, efficiency & high acceptability of misoprostol administered through vaginal route as a means to evacuate the uterus following a missed abortion. There are several statistically significant experimental differences between the oral and vaginal routes. Women receiving vaginal misoprostol experienced a shorter time to complete expulsion, less frequent surgical

intervention and fewer side effects than women taking the drug orally in a fixed dose.

In this study, a number of patients needed surgical evacuation in both groups, but one of the important observations is that all the patients who needed surgical evacuation had soft dilated cervix at the time of surgery, which reduced the risk of perforation & cervical injury.

From this small study, it is anticipated that vaginal administration of misoprostol is more effective and better tolerated than oral administration for the induction of first trimester abortion. So,when considering the treatment of missed abortion, policy makers should assess the relative costs of medical versus surgical treatment. Furthermore, misoprostol treatment of missed abortion can have an important role in reducing the occurrence of post surgical complications.

The potential role of a safe non surgical evacuation holds a tremendous promise. Misoprostol appears to achieve this promise and enable all of these women to avoid unnecessary surgical evacuation. Misoprostol treatment of missed abortion should be explored for introduction into health care delivery system nation wide.

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