

Intravaginal Misoprostol for Treatment of First Trimester Incomplete Miscarriages: A Randomised Controlled Trial

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Abstract

Objective: To compare the efficacy of medical evacuation using intravaginal Misoprostol 800 mcg eight-hourly in 24 hours with surgical evacuation in treating first trimester incomplete miscarriages.

Study design: Randomised controlled trial for one-year duration in a tertiary hospital. One hundred women with first trimester incomplete miscarriage were randomised to undergo either medical evacuation with intravaginal Misoprostol 800 mcg eight-hourly up to three doses or surgical evacuation.

Main outcome measures: Successful evacuation between intravaginal Misoprostol and surgical evacuation in treating first trimester incomplete miscarriages.

Results: Successful evacuation was achieved in 94% of patients undergoing medical evacuation with intravaginal Misoprostol compared to 98% in the surgical evacuation group ($p=0.617$). Duration of bleeding between both groups was not significantly different ($p=0.491$). There was a statistically significant drop in haemoglobin day 1 post treatment in the surgical evacuation group compared to Misoprostol group (0.7 g/dl vs 0.2 g/dl, $p=0.015$). There were more patients complained of diarrhea ($p=0.001$) and fever ($p=0.001$) in the Misoprostol group but this was minor and did not require any treatment.

Conclusions: Intravaginal Misoprostol 800 mcg eight hourly within 24 hours is an effective and safe alternative treatment to surgical evacuation in treating first trimester incomplete miscarriages.

Keywords: Misoprostol; Incomplete miscarriage; Randomised trial; Medical management

Introduction

Early pregnancy failure is not uncommon and it occurs in up to 20% of all recognized human pregnancies [1] and that one out of four women will experience at least one miscarriage in their lifetime [2]. It is of great concern especially in the low resource countries as it can result in excessive bleeding and infection with maternal morbidity and even mortality [3]. Furthermore, psychiatric morbidity after miscarriage like depression, and anxiety should be given due consideration [4].

Surgical curettage is the standard treatment for spontaneous miscarriages [5], which carry risks of uterine perforation, infections, intrauterine adhesions and cervical

trauma [2,6,7]. In addition, there are increased costs due to hospitalization and surgical treatment [8]. With this, expectant and medical management is getting more popular now.

With expectant management, however there is great uncertainty as to when complete evacuation will occur, thus, prolonged follow up is required to ascertain this. This is stressful for women. However, overall success rate for complete evacuation and the need for surgical evacuation are comparable for both expectant management and medical treatment as reported in a recent Cochrane review. The success rate for Misoprostol was 80-81% while expectant management from 52-85% [9]. When expectant management is compared to surgical evacuation, there were more cases of incomplete evacuation and unplanned surgical treatment in

the expectant group (28% vs 4%) [10]. The expectant group also experienced longer duration of bleeding and increased need for blood transfusion, however there were no differences in terms of pain or risk of infection both the two groups.

There is mounting evidence that medical evacuation with Misoprostol is an effective and safe alternative [9]. Misoprostol is a synthetic analogue of prostaglandin E1 used for prevention and treatment of peptic ulcer disease. It is cheap and easily stored at room temperature. However, because of its uterotonic and cervical ripening activity, Misoprostol had been used extensively despite off label [11]. This product can be used orally, intravaginally and sublingually and various doses and regimes have been used in treating miscarriages [12].

When compared to surgical evacuation, there was more incomplete evacuation with Misoprostol [9]. Misoprostol was found to have a success rate of 80-99% where as surgical evacuation achieving between 91-100%. Despite that, there was no significant different in term of women's satisfaction between Misoprostol and surgery [9].

The dosages used in the previous studies varied and the optimal dosage as well as the route of administration is still uncertain. Thus, the objective of this study is to compare the efficacy and safety of intravaginal Misoprostol 800 mcg 8 hourly for 24 hours to surgical evacuation in treating first trimester incomplete miscarriages.

Materials and Methods

Study design

This was a randomised controlled trial in a tertiary hospital for one-year duration. The study was approved by the University Medical Research and Ethics Committee. All women with first trimester pregnancy at less than 13 weeks' period of amenorrhoea were invited to participate in to the trial. Gestational age was confirmed by the last menstrual period and ultrasound. The diagnosis of incomplete miscarriage was made either after patient had aborted with opened cervical os or trans-vaginal ultrasound showed endometrial thickness (ET) of more than 15 mm.

The exclusion criteria were as follow:

- Medical history of cardiovascular, respiratory, liver, renal or sickle cell diseases
- History of previous uterine surgery
- Patient is haemodynamically unstable (90/50 mmHg \geq BP \geq 160/90 mmHg or PR \geq 110 bpm)
- Suspected sepsis with temperature \geq 38 oC
- Active genital infection
- Failed medical or surgical evacuation prior to presentation
- Known allergy to Misoprostol

Randomisation

All eligible women were informed regarding the study and consented were recruited into the trial. Patient who refused to participate were managed as per hospital protocol. A patient information sheet was provided to all the participants. Block randomization was used to ensure a balanced distribution in both study arms. Patients allocated in-group A were treated with intravaginal Misoprostol 800 mcg 8 hourly for 24 hours. Patients' in-group B were treated with surgical evacuation [evacuation of retained product of conception (ERPOC)]. It was not possible to blind the patient and researches due to the nature of the intervention.

Study procedure

The patient assessment included a vaginal examination and trans-vaginal ultrasound for ET measurement. A blood sample was obtained to determine haemoglobin, blood group and Rhesus factor. If Rhesus negative, 250 IU anti-D IgG was given.

Group A (Intravaginal Misoprostol): First dose of 800 mcg Misoprostol were administered intravaginally in the ward by the researches. Second and third dose were inserted 8 hourly apart by the medical officer on call if there was no product of conception passed. The timing of administration was recorded.

Group B (Surgical Evacuation): All patients in this group underwent ERPOC under anaesthesia in the operating theatre, performed by the medical officer on call. They were fasted until the operation.

Vaginal examination and trans-vaginal ultrasound was performed 24 hours after initiation of the first dose of intravaginal Misoprostolin in patient allocated to Group A. The same procedure was performed for patient allocated in Group B before discharge. The diagnosis of complete evacuation after treatment is defined as when the cervical os is closed on vaginal examination or ultrasound shows no more retained products of conception or an endometrial thickness of less than 15 mm.

If no or part of product of conception had passed out and ultrasound reveals endometrial thickness of more than 15 mm, a diagnosis of treatment failure was therefore made. Patient will thus require surgical evacuation and will be booked for ERPOC. All tissues were sent for histopathological examination (HPE). Before discharge, a haemoglobin check was done.

All patients were followed up and seen by the main researcher 14 days post evacuation to assess duration of bleeding, side effects, and complication, drop in haemoglobin and to review the HPE result. The main researcher was not blind to the treatment allocation during this visit.

Flow Chart

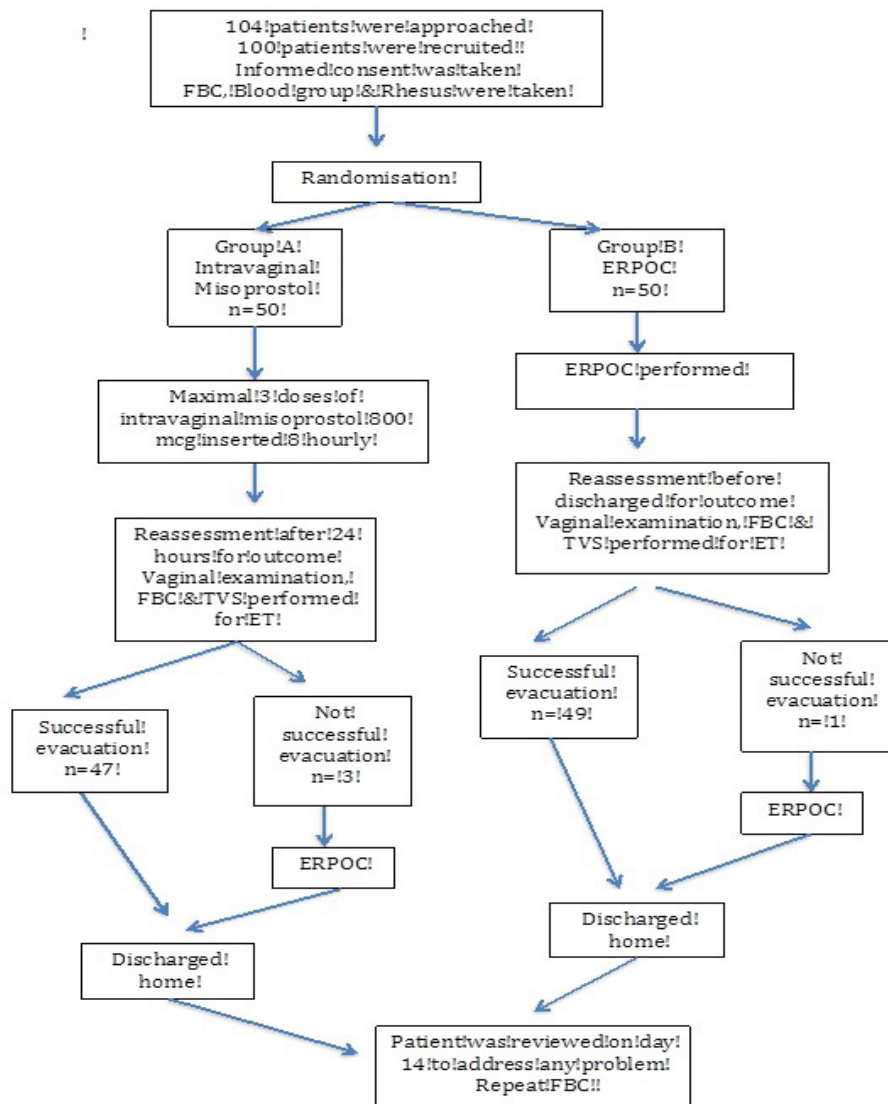


Figure 1

Statistical analysis

Analysis of the data was made using SPSS package version 16.0 statistical package. The non-normally distributed variables were evaluated with non-parametric test. Chi-square was used to compare the categorical variables, where as Mann-Whitney test was used to compare the continuous variables of the two groups.

Result

A total of 100 patients were eligible and consented to the trial. The baseline characteristic data were shown in the Table 1. They were comparable in maternal age; gestational age, ethnicity, haemoglobin pretreatment and ultrasound scan of endometrial thickness. The median age of patient was 30 years old in-group of intravaginal Misoprostol and 27.0 in surgical evacuation, which was not statistically significant ($p=0.302$). Majority of participants were Malays (77%) followed by Chinese (15%) and others (5%). There were no dif-

ferent in term of parity in both group ($p=1.000$), gestational age ($p=0.975$), Hb pre-treatment ($p=0.212$) and endometrial thickness from ultrasound ($p=0.273$).

The rate of successful evacuation was comparable ($p=0.617$) in both the intravaginal Misoprostol (94%) and surgical evacuation group (98%) (Table 2). Almost half of the patients (46%) required only two doses of Misoprostol 800 mcg eight hour apart before passing out POC (Table 3). There was no statistically significant difference with regards to duration of bleeding for both intravaginal Misoprostol and surgical evacuation groups (6.0 vs 7.0 days, $p=0.491$). The difference in reduction of haemoglobin level at day 1 post treatment was found to be statistically significant, with a lower reduction in the Misoprostol group (reduction of 0.2 vs 0.7 g/dl, $p=0.015$). However, there was no statistically significant difference when the reduction of haemoglobin was assessed again 14 days after discharged (reduction of 0.1 vs 0.4 g/dl, $p=0.259$) (Table 4).

	Overall	Intravaginal Misoprostol	Surgical Evacuation	Analysis
	(n= 100)	(n=50)	(n=50)	
Age (years)	28.0 (25.0,32.8)	30.0 (25.8,34.0)	27 (25.0,32.0)	Z=-1.033 p=0.302
Ethnicity, n (%)				
· Malays	77 (77.0)	41 (82.0)	36 (72.0)	
· Chinese	15 (15.0)	8 (16.0)	7 (14.0)	X ² =5.191
· Indians	3 (3.0)	0 (0.0)	3 (6.0)	p=0.158
· Others	5 (5.0)	1 (2.0)	4 (8.0)	
Parity, n (%)				
· 0	45 (31.0)	22 (44.0)	23 (46.0)	X ² =0.040
· ≥ 1	55(69.0)	28 (56.0)	27 (54.0)	p=1.000
Gestational age (weeks ± IQR)	10.0 (8.4,11.6)	10 (8.6, 11.5)	10.0 (8.3,11.7)	Z=-0.031 p=0.975
Hb pre-treatment (g/dl ± IQR)	12.3 (11.4,13.4)	12.4 (11.7,13.3)	12.1 (11.0,13.4)	Z=-1.249 p=0.212
Endometrial thickness (mm ± IQR)	23.5 (21.0,30.0)	24.0 (21.0,34.0)	22.5 (20.0,30.0)	Z=-1.096 p=0.273
All parameter expressed in median (quartile) unless specified				

Table 1: Baseline characteristics

	Overall (n= 100)	Intravaginal Misoprostol (n= 50)	Surgical Evacuation (n=50)	p-value
Successful evacuation, n (%)				
· Yes	96 (96.0)	47 (94.0)	49 (98.0)	χ ² =1.042
· No	4 (4.0)	3 (6.0)	1 (2.0)	p=0.617

Table 2: Study outcome

	Frequency	Percentage
1 dose	13	26
2 doses	23	46
3 doses	14	28
Total	50	100

Table 3: Requirement for misoprostol doses

	Overall n=100	Intravaginal Misoprostol n=50	Surgical Evacuation n=50	p-value
Duration of bleeding (days \pm IQR)	7.0 (5.0,7.0)	6.0 (5.0,7.0)	7.0 (5.0,7.0)	Z=-0.688 p=0.491
Reduction of Hb day 1 (g/dl \pm IQR)	0.4 (0.0,1.0)	0.2 (0.0,0.8)	0.7 (0.2,1.2)	Z=-2.431 p=0.015*
Reduction of Hb day 14 (g/dl \pm IQR)	0.2 (0.0,0.8)	0.1 (0.0,0.7)	0.4 (0.0,0.8)	Z=-1.129 p=0.259
*p < 0.05 All parameter expressed by median (quartile) unless specified				

Table 4: Other clinical outcome

	Overall n=100	Intravaginal Misoprostol n=50	Surgical Evacuation n=50	p-value
Nausea, n (%)	3 (3)	3 (6)	0 (0)	$\chi^2=3.093$ p=0.242
Vomiting, n (%)	2 (2)	2 (4)	0 (0)	$\chi^2=2.041$ p=0.495
Diarrhoea, n (%)	10 (10)	10 (20)	0 (0)	$\chi^2=11.111$ p=0.001*
Fever, n (%)	11 (11)	11 (22)	0 (0)	$\chi^2=12.360$ p=0.001*

*p < 0.01

Table 5: Side effects of both study groups within 24 hours

Side effects of Misoprostol include nausea, vomiting, diarrhea and fever. All the side effects were minor and did not require any treatment except one patient whose had prolonged fever for four days and was admitted and treated with intravenous antibiotic for suspected endometritis. However, this was not proven by culture and sensitivity from the high vaginal swab. Both diarrhoea and fever were found to

be statistically significant in Misoprostol group as compared to surgical evacuation group. (p=0.001) (Table 5). There was no major complication in either group during the period of study such as uterine perforation, excessive haemorrhage or sepsis.

After discharge from hospital, a patient in intravagi-

nal Misoprostol group had mild abdominal pain and another patient had headache for seven days. Both required treatment with Paracetamol only. One patient in surgical evacuation group complained of mild dizziness for seven days. Another patient in same group was still having per vaginal spotting, however a repeat ultrasound showed no significant finding. In both cases, anaemia was excluded.

Discussion

Surgical evacuation for treatment of spontaneous first trimester miscarriage has been established. It has been recognized as a standard treatment in many parts of the world with the success rate of 91-100% [9]. This procedure is not without risk or complication. However, the risk is small in experienced hands.

Alternatives are expectant and medical management that are gaining more popularity recently. Expectant management allows for spontaneous abortion that follows the natural history of miscarriage. The success rate of expectant management is reported to be between 25-85% [13-15]. This is consistent with the recent Cochrane review by Neilson et al. [9]. However, the time needed for complete evacuation varies. A study showed that 40% women who opted for expectant management, 60% of them would change their decision after 48 hours [14]. This might be due to the longer duration of persistent per vaginal spotting and risk of blood transfusion [10]. Besides that, expectant management group was more likely to have incomplete evacuation and unplanned surgical treatment (28%) as compared to the surgical evacuation group (4%).

Medical management with various abortifacients is gaining popularity with success rates of 13 to 96% [16,17]. This is due to different study protocols using different patient populations, different combination therapy, and different type of prostaglandins, dosages and routes of administration. The type of miscarriages also differ i.e. missed miscarriage [18,19], incomplete miscarriage [16] or all types of early pregnancy failures was recruited [20,21]. In some studies, combination of mifepristone followed by prostaglandin administration was used [20,22]. Study using sulproston and Misoprostol also has also been reported [17].

With regards to the Misoprostol dosage and route of administration used, single dose of oral Misoprostol 400 mcg gave the lowest success rate of only 62% when given three times a day (23). Studies using vaginal Misoprostol for treatment of miscarriage reported higher success rates up to 88% [19,21]. In our study, we used intravaginal Misoprostol 800 mcg 8 hourly up to three doses and we achieved success rate of 94%, which was comparable to surgical evacuation. This success rate was higher than study done by Tang et al. that used 600 mcg of vaginal Misoprostol 3 hourly for maximal of three doses that reported success rate of 88% [12]. When compared with surgical evacuation, the success rate of medi-

cal treatment is reported between 80-99% and surgical evacuation achieving between 91-100% [9].

The common side effects of Misoprostol being reported are abdominal pain, nausea, vomiting, diarrhea and fever. They are dose-dependent and related to type of prostaglandin used [24]. These side effects were reported in our study. Ten (20%) patients in the intravaginal Misoprostol group had diarrhea compared to none in the surgical evacuation group within the first 24-hour period. This is less compared to 38% of patients in the study by Crenin et al. [21]. The frequency and intensity of side effects encountered would have been worse if the route was oral. There were 50% of patients receiving oral Misoprostol who had diarrhea in the same study by Crenin et al. [21].

In our study, the duration of vaginal bleeding post-treatment between the two groups did not differ significantly ($p=0.491$). This finding is consistent with the review by Demetroulis et al. [25]. The reduction in haemoglobin level is also significant in favour of intravaginal Misoprostol group at day 1 post-treatment but not at day 14. These findings were different as compared to previous studies done by Demetroulis as they found that there were no significant drops in the haemoglobin levels post treatment between the two groups. A possible reason for the reduction of haemoglobin at day one post treatment might be that as the patient was fasted with intravenous drip, this caused haemodilution. In this case, assessment of reduction of haemoglobin level probably more accurate at day 14 after-treatment.

Limitation

The time period taken from Misoprostol insertion to passing out POC was not assessed in this study. This information would have been useful so that patient's satisfaction will be improved and thus compliance can be enhanced if medical termination is used in outpatient setting. Patient's satisfaction with the different treatment was also not assessed.

Conclusion

In conclusion, intravaginal Misoprostol is a safe and efficacious alternative treatment for incomplete miscarriage. Another randomized controlled trial assessing the efficacy and safety of outpatient Misoprostol for treatment of spontaneous incomplete miscarriage had been completed in our centre and is in the process of being written.

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Ethic Committee Approval

This study was approved by UKM Research Ethics Committee (UKMREC) and given the project code FF-159-2005. Funding for the project came from UKM Grant.

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