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ORIGINAL ARTICLE

A Randomized Trial of Misoprostol Compared with Manual Vacuum Aspiration for Early Pregnancy Failure

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Abstract

Aims: To compare the efficacy of vaginal misoprostol and manual vacuum aspiration for the treatment of early pregnancy failure.

Methods: A total of 180 women with a first trimester pregnancy failure were randomized to treatment with either 800μg of misoprostol vaginally or manual vacuum aspiration in a 2:1 ratio. The misoprostol group received treatment on the day of admission (day 1), a second dose of 800μg on day 3 if expulsion was incomplete and surgical management on day 8 if expulsion was still incomplete. Surgical aspiration in the misoprostol group and repeated aspiration in the manual vacuum aspiration group within 30 days of initial treatment constituted treatment failure.

Results: Out of 120 women assigned to get misoprostol, 69 % had complete expulsion by day 3, and 82 % by day 15. Treatment failed in 18 percent of the misoprostol group and 2 percent of the surgical group by day 15. The risk of haemorrhage was 10 % in the misoprostol group and 7 % in the surgical group (P = 0.584; R.R 1.5, 95 % CI 0.505 – 4.455). Pelvic infection represented by fever was similar in both groups. In the misoprostol group 53 % women had nausea as compared to 28 % in the surgical group (P = 0.002, RR 1.852 95 % CI 1.196 – 2.868). In the misoprostol group, 78 % of the women stated that they would use this again if needed, and 83 % would recommend this to others.

Conclusions: Treatment of early pregnancy failure with 800μg of vaginal misoprostol gives 82 % success rate and is acceptable.

Key words: Miscarriage, misoprostol, vacuum aspiration randomized trial

Introduction

About 15 percent of clinically recognized pregnancies end in early pregnancy failure Early pregnancy failure in first trimester includes early foetal loss (missed miscarriage or blighted ovum) and retained products of conception (incomplete abortion)[1]. In our setup the kind of population of early pregnancy failure is different from that we find in developed countries. Incomplete and inevitable miscarriage cases are much more than cases with anembryonic gestation or fetal death. Once diagnosis is established evacuation of uterus is usually done by surgical methods like suction evacuation or manual vacuum aspiration as soon as possible to decrease the risk of infection and bleeding. These methods are not free from risks. It may be associated with various complications like cervical injury, uterine perforation, and pelvic infection, risk of anesthesia, excessive bleeding and intrauterine adhesions. These complications become even more serious if the surgical evacuation is done by unskilled and unqualified personnel. The incidence of septic miscarriage getting admitted to this hospital is 6.59% of which surgical evacuation being commonest (84%) method used which led to septic miscarriage and untrained person performing surgical evacuation in 68% cases[2].

Misoprostol (800 μg) given vaginally for treatment

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of early pregnancy failure is safe, acceptable and has about 84% success rate[3].

In fact success rates following medical management of early pregnancy failure have been reported between 13% and 96%[4,5].

Royal College of Obstetrician and Gynecologist Guideline 2006 suggests that medical evacuation has economical benefits and those selection criteria for medical evacuation should be developed in individual units[6].

We therefore decided to compare misoprostol treatment with vacuum aspiration for cases of early pregnancy failure in our population.

Methods

Settings: The study was conducted at R.G Kar Medical College and Hospital, Kolkata, India between 1st May 2007 and 30th April 2008.

Subjects:
Subjects were women admitted for medical care for possible early pregnancy failure. Women with anembryonic gestation or embryonic or fetal death were included if their ultrasound finding showed an embryonic pole of crown rump length between 5 and 40mm without cardiac activity or an anembryonic gestational sac with a mean diameter between 16 and 45mm women with incomplete spontaneous miscarriage diagnosed clinically by passage of some product of conception and sonographically by endometrial lining exceeding 30mm and uterine size less than 12 weeks of gestation were included[7,8]. Women who had inevitable miscarriage diagnosed sonographically with intrauterine gestational sac of less then 45mm or embryonic pole of less than 40mm and internal cervical os open to digital examination with active vaginal bleeding were also included in our study. Women were excluded if they were haemodynamically unstable, had hemoglobin level less than 8gm percent, had history of coagulation disorder or were on anticoagulant (including aspirin), were allergic to misoprostol and did not give history of medical or surgical intervention by other medical personnel in this current pregnancy. All subjects who gave written informed consent were recruited.

Procedural Steps:
At admission (and enrollment) detailed medical history, physical examination, necessary investigation was done using a previously written case data sheet. Eligible subjects were randomly assigned to either medical or surgical management in a 2:1 ratio. The day of randomization (admission day) was considered day 1 of study. It was simple randomization taken from computer generated random number list. Allocation concealment was done by opaque sealed envelop. Investigator in charge of sequence generation and preparation of envelop was not involved in the clinical assessment of the subjects. Outcome assessors of the study were blinded.

Women assigned to medical treatment were given 800µg of misoprostol vaginally into the posterior fornix on day 1. On day 3 Trans Vaginal Sonography was done to find out if expulsion of product of conception was complete and if so she was discharged from the hospital. If it was found that uterus was not evacuated completely (by visualization of gestational sac, product of conception or endometrial lining > 30mm) a second dose of 800µg of misoprostol was administered vaginally. On day 8 if it was still incomplete vacuum aspiration was done to complete the procedure.

Women assigned to surgical treatment had to undergo manual vacuum aspiration under intravenous sedation in Operation Theater by the post graduate trainee under supervision and discharged next morning after evaluation by ultrasonography and haemoglobin estimation. Surgical procedure was done by manual vacuum aspirator (Ipas MVA plus aspirator) with easy grip cannulae of different sizes attached to it accordingly. Blood transfusion was given before discharge if there were a fall in haemoglobin by 3 gm/dl or more.

Women treated with misoprostol who were discharged on day 3 and women treated with manual vacuum aspiration who were discharged on day 2 were communicated telephonically on day 8 for their wellbeing. Symptoms like vaginal bleeding, temperature and pain abdomen was enquired.
Pain intensity was recorded by VAS scale with higher numbers indicating greater pain. They were asked to keep a record of their body temperature daily for two weeks, and to attend emergency whenever they would feel for the same because of any emergency condition.

All the patients returned for follow up on day 15 when they were enquired again about their problems. They were examined physically; along with hemoglobin estimation and Trans Vaginal Sonography. Each woman completed a questionnaire assessing the acceptability of the treatment. On day 30 a telephonic interview was conducted to know their wellbeing and if any additional treatment was taken by any woman.

Statistical analysis: Success was defined as complete uterine evacuation without need for vacuum aspiration

in the medical management group and without need for repeat aspiration in the surgical management group.

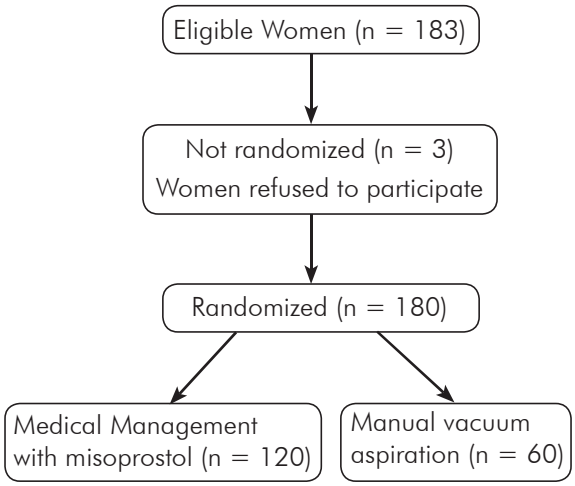
For calculation of sample size it was assumed on the basis of clinical judgments that 15 % difference in success rate in the management of early pregnancy failure between two groups is meaningful difference and it is estimated that 120 subjects in the misoprostol group and 60 subjects in surgical management group (aiming for 2:1 randomization) would be required to detect this 15 % difference with a 80% power and 5% probability of type 1 error. Success rate in misoprostol group assumed to be 78%.

Success rate of categorical variables was compared between group by Fisher's exact test / chi-square test as appropriate. Numerical variables was compared between two groups by student unpaired't' test. All statistical analysis were done by Graph pad prism version 4 (Graph pad Software Inc, 2005) and Statcalc version 5 (Ace Stat Software, 2003).

Ethical Consideration:

The study was approved by the committee for Ethical Consideration and Approval for Human Research, R.G Kar Medical College and Hospital as required by Indian law. Before enrollment for the study entry, all women provided a writer informed consent meeting all local institutional requirements.

Results



A total of 183 women were enrolled of which 120 were randomly assigned to receive misoprostol where as 60 were randomly assigned to undergo vacuum aspiration. Three women refused to participate in this study. At enrollment, the demographic characteristics did not vary significantly in the two groups of women (Table 1).

Table 1. Characteristics of the study population at enrollment

CHARACTERISTIC		MISOPROSTOL (N=120)	Surgical management (N=60)
1. Age-yr		23.57+ 4.79	23.86+4.74
2.Education	S	104	50
	HS	13	1
	AHS	3	9
3.No of previous	0	63	23
pregnancies %	1	27	22
	2	30	15
4. Planned pregnancies no %		42	21
5.Best estimate of gestational age-wk		7.33+1.92	7.30±1.87
6.Lower abdominal pain/24hr		74	33
7.Vaginal bleeding /24hr		81	39
8.Pregnancy failure			
type	IM	77	37
	IEM	36	19
	FD	4	2
	AG	3	2
9.Haemoglobin –g/dl		10.03±1.63	10.1±1.62

S- Secondary, H.S.- Higher Secondary, A.H.S. – Above Higher Secondary
I.M. – Incomplete miscarriage, IEM – Inevitable miscarriage, F.D. – Faetal Death
A.G. – Anembryonic Gestation

Table 2. Efficacy of the treatment with misoprostol

	With misoprostol	with manual Vacuum Aspiration (Surgical evacuation)	P valu*in comparison to surgical evacuation	RR in comparison to surgical evacuation
Success rate by time after intervention				
By day3	83 / 120 (69.17%) (95% Cl 60.90 - 77.43%)	—	—	—
By day 8	98 / 120 (81.67%) (95% Cl 74.74 - 88.59%)	—	—	—
By day 15	98 / 120 (81.67% (95% Cl 74.74 - 88.59%)	59/60 (98.33%)	<0.001	0.83 (95% Cl 0.758 - 0.909)
Success by type of early pregnancy failure				
Incomplete miscarriage	63 / 77 (81.82%)	37 / 37 (100.0%)	0.004	0.82 (95% Cl 0.736 to 0.909)
Inevitable miscarriage	32 / 36 (88.89%)	19 /19 (100.0%)	0.286	0.89 (95% Cl 0.792 to 0.998)
Anembryonic gestation	1 / 3 (33.33%)	2 / 2 (100.0%)	0.400	0.33 (95% Cl 0.067 to 1.652)
Fetal death	2 / 4 (50.00%)	1 /2 (50.0%)	1.000	1.00 (95% Cl 0.183 to 5.462)
Success by gestational age in week				
4 weeks	8 / 11 (72.73%)	5 / 5 (100.0%)	0.509	0.73 (95% Cl 0.506 to 1.045)
6 weeks	40 / 49 (81.63%)	25 / 25 (100.0%)	0.024	0.82 (95% Cl 0.715 to 0.932)
8 weeks	24/29 (82.76%)	15 / 16 (93.75%)	0.399	0.88 (95% Cl 0.716 to 1.088)
10 weeks	26 / 31 (83.87%)	14/14 (100.0%)	0.305	0.84 (95% Cl 0.719 to 0.979)

**Denotes 2 tailed P value from fisher's exact test*

The success rate data of the two modalities of treatment are presented in Table 2.

By day 15, 82% women (95% confidence interval, 75 to 89 percent) were successfully treated with misoprostol and 98% women (95% confidence interval 95 – 102 percent) were successfully treated with vacuum aspiration.

In the misoprostol group the success rate after one dose was 69% which increased to 82% after the second dose. Success rate varied among the subtypes of early pregnancy failure. Women with an anembryonic gestation had the lowest success rate (33%) by day 8.

Different adverse events of the two methods and their acceptability are shown in table 3.

The incidence of adverse events like hemorrhage, fever and abdominal pain was similar in the two groups. Only the incidence of nausea was significantly higher (P = 0.002) in the misoprostol group. Women undergoing vacuum aspiration had less diarrhoea than who had taken misoprostol (P = 0.073). The acceptability of treatment did not differ significantly between the two groups.

Table 3. Adverse Events and Acceptability of Treatment

VARIABLE	MISO (N=120)	Surgical management (N=60)	P Value	RR	95% CI
1. Haemorrhage with fall in hemoglobin by ≥ 2 gm/dl	12(10%)	4 (7%)	0.584	1.500	0.505-4.455
2. Cervical tear/ perforation	0	0	-------	-------	----------
3. Fever *	5(4%)	2(3%)	1.000	1.250	0.249-6.257
4. Emergency Visit	5 (4%)	2(3%)	1.000	1.250	0.249-6.257
5. Fall in hemoglobin by ≥ 2 g/dl	9(80/o)	3(5°/o)	0.753	1.500	0.421-5.339
6. Fall in hemoglobin by ≥ 3g/dl Blood transfusion	3(3%)	1(2%)	1.000	1.500	0.159-14.123
7. Nausea - %	63(53%)	17(28%)	0.002	1.852	1.196-2.868
8. Diarrhea - %	28(23%)	7(12%)	0.073	2.000	0.927-4.312
9. Abdominal Pain - % •	118(98%)	57(95%)	0.335	1.035	0.972-1.101
10. Analgesic	8(7%)	3(5%)	0.753	1.333	0.366-4.846
11. Would recommend this procedure	100(83%)	50(83%)	1.000	1.000	0.870-1.148
12. Would use this treatment again	93(78%)	45(75%)	0.712	1.033	0.867-1.231

* *Temperature of ≥ 38° C recorded after 24 hrs of insertion of misoprostol, upto the end of 2nd week.*

• *A 10cm visual analogue scale (VAS) was used to record severity of pain. Higher number indicated more pain. Analgesic was given with higher pain score*

Discussion

In developing country like India, surgical evacuation is the standard treatment of early pregnancy failure, partly because of concerns about the risk of pelvic infection and partly because of lack of knowledge and experience regarding medical treatment with misoprostol. Misoprostol, a medical alternative to surgical evacuation is an orally active prostaglandin analogue that is cheap, easy to administer and stable at room temperature.

However access to the safe surgical procedure is often not possible because of lack of skilled personnel and facilities.

In these setting misoprostol could save many lives annually even at rural health centers. Our study showed that treatment of early pregnancy failure with 800µg of misoprostol vaginally, with the dose repeated after 48 hours when necessary is quite effective. The success rate by day 15 was 82 % (95 % CI 75 - 89 %). We have found that 800µg of misoprostol used vaginally was sufficient in the majority (69 %) of women and only in 31 % of cases it had to be repeated after 48 hours.

Medical treatment of early pregnancy failure has been reported to have success between 13% and 96%[4,5]. This variation may be due to several factors like patient selection, type of early pregnancy failure, the dosage and route of administration of misoprostol, concomitant use of mifepristone etc.

A randomized trial comparing expectant with medical management for first trimester miscarriages showed that expectant management is almost as effective as the medical treatment[9]. But gyanecological infection was thought to be of concern with expectant management. However a large randomized controlled trial has convincingly shown that the incidence of gynecological infection after surgical, expectant and medical management of first trimester miscarriage was low and not significantly different[10].

The population of patients with early pregnancy failure in our setting is quite different from that in developed countries[3]. Majority women had incomplete or inevitable miscarriage (95 out of 120 in the misoprostol group and 56 out of 60 in the surgical group) while a study in developed country showed their population

consisting more women with anembryonic gestation and fetal death though the criteria to define those conditions were similar[3].

This may be because ultrasound is not routinely done in the first trimester in our country population. So the cases with anembryonic gestation or fetal death does not visit a doctor in the first trimester until there is a problem in terms of vaginal bleeding or spotting or cramping when majority gets converted to incomplete or inevitable miscarriage type of early pregnancy failure.

We have found that women with an incomplete or inevitable miscarriage were more likely to have complete expulsion (82% & 89%) than women with embryonic death or anembryonic gestation (50% & 33%). We waited for 48 hours between doses in an attempt to allow sufficient time for the initial dose to be effective while acknowledging the desire for prompt uterine evacuation. The majority of women reported satisfaction with this approach.

Though women treated with misoprostol had significantly higher incidence of nausea as compared with women treated by surgical management, still they managed to tolerate.

None of the woman in our study was lost to follow up.

It is yet to be found out whether 800µg of misoprostol is the lowest effective dose for all subtypes of early pregnancy failure. Many women with early pregnancy failure were not recruited in our study as they were either anaemic (haemoglobin level less than 8gm %), haemodynamically unstable due to excessive bleeding or gave history of medical or surgical intervention by other medical personnel in this pregnancy. This however limits the generalisability of the results.

In our study all women were treated after admission to the hospital. Future studies should address the appropriate application of medical therapy by misoprostol outside the tertiary facilities and development of out patient management protocols.

Conclusion

Misoprostol treatment can be a better alternative to surgical management for early pregnancy failure if clear instruction can be given to women, for monitoring bleeding, infection and by making emergency service readily accessible.

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