RANDOMISED CONTROLLED TRIAL OF THE EFFICACY OF MISOPROSTOL USED AS A CERVICAL RIPENING AGENT PRIOR TO TERMINATION OF PREGNANCY IN THE FIRST TRIMESTER

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Background. Misoprostol is being used increasingly in clinical practice for cervical ripening in first-trimester abortions, but because of lack of good evidence of its effectiveness, administration consensus has not been reached on dosage, route of administration, time of administration pre-operatively and gestational age group. In this study we tested the hypothesis that self-administration of 600 μg vaginal misoprostol is feasible and when used 2 - 4 hours pre-operatively results in sufficient cervical dilatation to make suction curettage easier.

Methods. A double-blind, randomised, placebo-controlled trial was undertaken. Two hundred and seventy-eight women scheduled for termination of pregnancy of up to 12 weeks' duration by manual vacuum aspiration were assigned to receive either 600 μg misoprostol pre-operatively, or placebo. The achievement of 'satisfactory' (≥ 7 mm) baseline cervical dilatation after 2 - 4 hours was evaluated as the primary outcome. Secondary outcome measurements included ease and duration of the procedure. Side-effects such as pre-operative bleeding, gastro-intestinal complaints and pain as well as adverse events were noted in all cases.

Findings. Self-administration of vaginal misoprostol was successful in all women and 273 women were evaluated for main end-points. A significantly larger proportion of patients in the treatment group reached cervical dilatation of ≥ 7 mm (67.3% v. 30.9%, $P < 0.0001$). The side-effects were minimal and comparable in the two groups. In the treatment group the mean procedure duration was significantly shorter (220 seconds v. 321 seconds, $P = 0.0013$) and the procedure was more likely to be rated by the operator as 'easy' (81.8% v. 63.3%, $P = 0.0082$). This resulted in a significant reduction in treatment failure in the < 70-day gestation group (5.0% v. 14.7%, $P = 0.005$).

Conclusion. It is feasible, safe and effective for 600 μg misoprostol to be self-administered vaginally 2 - 4 hours pre-operatively for cervical priming prior to manual vacuum aspiration. Further research is needed to establish optimal use in the first trimester and to determine patient acceptance.

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In the first 2 years following the enactment of a liberalised abortion legislation in February 1997, an estimated total of 50 000 terminations of pregnancy (TOPs) were performed in South Africa.[1] Two-thirds of women presented in the first 12 weeks of gestation, defined as the first trimester of pregnancy. Suction curettage by manual vacuum aspiration, usually under non-opioid analgesia,[2] has been the standard method used for first-trimester TOPs and is performed by both doctors and trained midwives. This technology has enabled decentralisation of abortion services within appropriate low-care settings, which has been essential in order to make the service accessible and economically feasible. An additional feature in the management of first-trimester TOPs in South Africa has been the widespread use of misoprostol for cervical ripening. As a result of a directive in the clinical guidelines (Gauteng Department of Health policy document, unpublished) accompanying the implementation of the new abortion law in 1997, many institutions issue misoprostol to be taken at home the night before the scheduled vacuum aspiration (i.e. off-site).

Over the last 5 years several clinical trials on the use of misoprostol for cervical ripening have been published,[3-9] but consensus has not been reached on the optimal dose, route of administration or time of administration pre-operatively. This partly reflects a lack of evidence from randomised controlled trials. Although el-Rafaey *et al.*[10] found a significant difference between misoprostol and placebo in cervical dilatation after administration of 600 μg misoprostol per vagina 2 - 4 hours pre-operatively in women who were 10 - 12 weeks pregnant, the difference was not sufficient to be of clinical importance.

This study was undertaken to test the feasibility, safety and effectiveness of the pragmatic use of misoprostol for cervical ripening in first-trimester TOP, namely self-administered vaginally 2 - 4 hours before manual vacuum aspiration performed by trained midwives. When considering an

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application to register misoprostol for use as a cervical primer in TOPs, the South African Medicines Control Council also identified the need for further evidence of its safety and effectiveness.

METHODS

Patients

Study patients were recruited between July and October 1998 at Kalafong Hospital, Pretoria from women booking at the TOP unit. Women were eligible for the study if they had a positive urine pregnancy test, a pregnancy of less than 13 weeks' gestation measured by ultrasound, and were requesting a legal TOP. Exclusion criteria included any women with symptomatic asthma or cardiac disease, conditions requiring anticoagulant therapy, a haemoglobin concentration of 8 g/dl or less, or other serious medical conditions. The study was approved by the Ethics Committee of the University of Pretoria. All women participating in the trial gave written informed consent.

Design

Women were counselled and assessed by staff at the TOP unit and given a date for the procedure. On the day of the procedure they were invited to participate in the study and were randomly assigned 600 μg misoprostol (Cytotec; Searle) or 750 mg ascorbic acid (in each case this was three tablets). Ascorbic acid was chosen as the placebo as a preparation was available that looked similar to misoprostol and it was known to dissolve in the vagina with no known effects on the cervix. Both drugs were white tablets of similar size. Misoprostol is hexagonal whereas the ascorbic acid tablet is round. The patient blinding was therefore based on the assumption that women requesting a TOP were misoprostol-naïve. Operator blinding was assured as moistened tablets dissolve quite rapidly at the edges making them appear round. The women were given the tablets in a sealed envelope and were instructed to go to a private room, open the envelope, hold the tablets between thumb and index finger under a running tap for approximately 10 seconds (which is known to facilitate the dissolving of the tablets in the vagina), and insert the tablets as high as possible into the vagina. They were then asked to wait for the procedure, and were advised that this would be in 2 - 3 hours' time. All women underwent surgical curettage using manual vacuum aspiration under paracervical regional block.

The procedures were performed in a treatment room adjacent to the gynaecology ward by five operators, four trained midwives and a doctor. Discussion with the operators and observations in the operating room by a Medical Research Council monitor revealed that in most cases the tablets had completely dissolved before the procedure, and if this was not the case, only a small white tablet residue could be seen, which was indistinguishable. The primary outcome was cervical dilatation as measured by Hegar dilators. Cervical dilatation was estimated as the largest Hegar dilator that would pass the internal os without resistance. This measurement was made by applying incrementally smaller dilators into the cervix until the dilator passed easily into the uterus. All outcomes and observations were recorded on a data capture sheet by a colleague. The rescue protocol for treatment failures (inability to dilate the cervix) consisted of a repeat dosage of 400 μg misoprostol administered orally 12 hours before the procedure, which was then scheduled for the following day. Women were discharged 1 - 2 hours after the procedure if there were no complications. Any complications were recorded and managed appropriately. Patients were advised to return to the TOP unit should problems arise after discharge. Post-discharge complications were also recorded.

Sample size

The primary outcome was measured using Hegar dilators and was dichotomised as being sufficiently large (7 mm or more) or insufficiently large for ease of performance of the procedure. In calculating the sample size it was assumed that given an estimated placebo effect of 30% of women achieving sufficient cervical dilatation, 50% of women achieving sufficiently large cervical dilatation in the treatment group was considered to be clinically significant. A sample of 270 women (135 women per group) was required in order to detect a 20% difference with 90% power using the 5% significance level.

Randomisation

For the first 152 women randomisation was done using random permuted size 8 blocks. This resulted in 76 women being randomised to receive misoprostol, and 76 placebo. Subsequently women were randomised without using random permuted blocks; a further 118 women were randomised in this fashion, with 56 receiving misoprostol and 62 receiving the placebo. Initially the data capture sheets for patients numbered 177 to 184 were mislaid, so these numbers and treatments were re-allocated to new patients. The forms for the original patients were recovered and the new patients were then given patient numbers 277 to 284 (with 277 receiving the same treatment as 177, 278 receiving that of 178, etc.). This meant that a further 3 women were randomised to receive misoprostol and 5 to receive the placebo. Consequently in total 135 women were randomised to receive misoprostol and 143 to receive placebo. The randomisation as specified was done by the trial statistician. The drugs were packed into envelopes at the Medical Research Council and labelled with trial numbers. The code details were kept at the Medical Research Council.

Statistical analysis

Analysis was by intention to treat. Data were entered twice using Epi-Info, and the databases were compared and connected until there were no discrepancies. The data were then exported for analysis using the statistical software SAS.

The primary outcome was the size of dilatation as measured by Hegar dilators. The dilatation was dichotomised as being 'sufficiently large' (7 mm or more), or 'insufficiently large' (less than 7 mm). Groups were compared for the proportion of women for whom the dilatation was sufficiently large. Efficacy conclusions were based on this outcome using the above technique.

Secondary outcomes analysed were the presence of bleeding or products of conception, the ease of procedure (on a 5-point ordinal scale), length of time to complete the procedure, the proportion of patients experiencing adverse events and the proportion of patients experiencing major adverse events. The groups were compared for these outcomes using the chi-square test and *t*-test. We also performed a subgroup analysis according to gestational age in order to determine whether the ripening effect of misoprostol was still clinically significant after 10 weeks of gestation.

RESULTS

A total of 278 consecutive women were recruited into the study (Fig. 1). The baseline characteristics of the 273 women for whom outcome data were available were similar with regard to the various co-variables (Table I). None of the women experienced difficulty in inserting the tablets. Analysis for primary outcome showed overwhelming evidence that women receiving misoprostol were more likely to achieve satisfactory cervical dilatation than women in the placebo group (Table II). There was overwhelming evidence of an overall treatment effect ($P = 0.0008$), with misoprostol being more likely to lead to a favourable outcome.

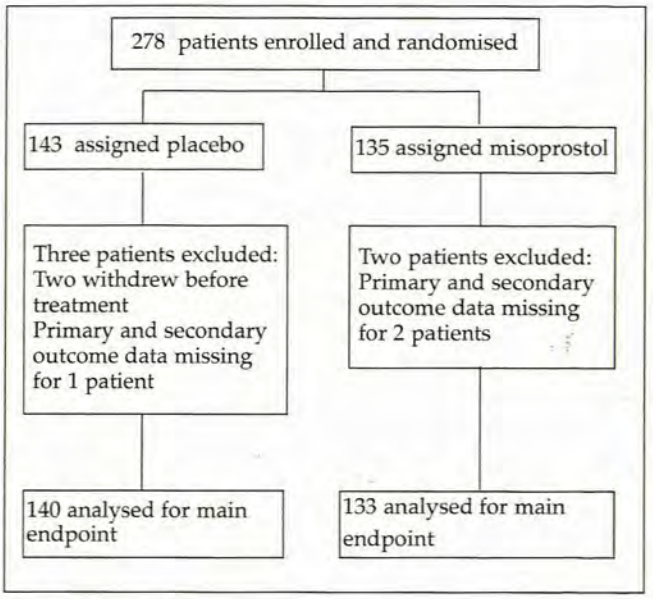

Fig. 1. Trial profile.

Table I. Baseline characteristics

Characteristics	Misoprostol ($N = 133$)	Placebo ($N = 140$)
Age (yrs)		
Mean (SD)	27.4 (6.85)	27.5 (6.75)
Parity		
Median (IQR)	1 (1 - 3)	1 (1 - 2)
Mean (SD)	1.81 (1.57)	1.68 (1.49)
Gravidity		
Median (IQR)	3 (2 - 4)	2 (2 - 3)
Mean (SD)	2.82 (1.55)	2.71 (1.65)
Gestational age (days)		
Mean (SD)	61.9 (9.67)	61.6 (8.52)
Number of previous TOPs (%)		
None	123 (93%)	129 (93%)
One	8 (6%)	6 (4%)
Two or more	1 (1%)	4 (3%)
Gestational age*		
< 69 days	101 (75.9%)	110 (78.6%)
≥ 70 days	32 (24.1%)	30 (20.8%)
Operator		
A	32 (51.6%)	30 (48.4%)
B	26 (50.0%)	26 (50.0%)
C	34 (44.7%)	42 (55.3%)
D	23 (46.0%)	27 (54.0%)
E	19 (51.4%)	18 (48.7%)

* $\chi^2 = 0.27$, $P = 0.60$, Fisher's exact test $P = 1.0$.
SD = standard deviation; IQR = interquartile range.

The results for the secondary outcomes showed that women on misoprostol were much more likely to experience bleeding and products of conception in the vagina than controls ($P < 0.0001$). The use of misoprostol also shortened the length of the procedure significantly and resulted in a procedure that was rated 'easy' in a significantly higher proportion of women (Table III). Side-effects and adverse events were minimal and comparable in the two groups, with the exception that significantly more women in the misoprostol treatment group experienced pre-operative pain (Table IV). However, none of these women required additional analgesia. No serious adverse events were experienced. In 3 women the abortion was incomplete and re-evacuation was necessary; 1 of them had received misoprostol and 2 the placebo. In 1 of these 2 cases the unsatisfactory nature of the evacuation was evident before discharge, so re-evacuation under general anaesthetic was performed prior to discharge. The operative procedure was impossible in 23 patients (7 misoprostol, 16 placebo), and these women were managed according to the rescue protocol. In 1 of the 7 women in the misoprostol group, the oral misoprostol resulted in sufficient cervical softening to enable manual vacuum aspiration to be performed. Oral misoprostol was successful in 9 of the 16 women in the placebo group. The 13 women who did not respond to oral misoprostol then underwent the procedure under general anaesthesia in an operating theatre.

Table II. Dilatation of the cervix as primary outcome measurement

	Misoprostol ($N = 133$)	Placebo ($N = 140$)	P-value
All cases			
Median (IQR)	8 (6 - 9)	6 (6 - 7)	
Mean (SD)	7.61 (2.13)	6.01 (1.80)	
Satisfactory dilatation (Hegar ≥ 7 mm)	92 (69.2%)	53 (37.9%)	< 0.001*
Unsatisfactory dilatation (< 7 mm)	41 (30.8%)	87 (62.1%)	
Gestation < 69 days			
Median (IQR)	7 (6 - 8)	6 (5 - 7)	
Mean (SD)	7.47 (2.18)	5.75 (1.87)	< 0.0001†
Satisfactory dilatation	68 (67.3%)	34 (30.9%)	
Unsatisfactory dilatation	33 (32.7%)	76 (69.1%)	
Gestation ≥ 70 days			
Median (IQR)	8 (6 - 9)	7 (6 - 7)	
Mean (SD)	8.06 (1.93)	6.97 (1.07)	
Satisfactory dilatation	24 (75.0%)	19 (63.3%)	0.32‡
Unsatisfactory dilatation	8 (25.0%)	11 (36.7%)	

* $\chi^2 = 26.86$; Fisher's exact $P < 0.0001$; OR 3.68; 95% CI (2.16; 6.29).
† $\chi^2 = 27.96$; Fisher's exact $P < 0.0001$; OR 4.61; 95% CI (2.48; 8.60).
‡ $\chi^2 = 0.99$; Fisher's exact $P = 0.41$; OR 1.74; 95% CI (0.51; 5.97).

The subgroup analysis showed that the effect of misoprostol on cervical dilatation depended on gestational age (Table II). If we treat the gestational age groups as strata, we can use Woolf's test to see whether the odds ratio (OR) for a satisfactory outcome for misoprostol versus placebo is constant over the strata.[11] The test statistic for homogeneity of ORs is $\chi^2 = 7.38$ on 1 df ($P = 0.0066$). There is therefore very strong evidence that the OR is not homogeneous over the two groups, i.e. gestational age modifies the effect of misoprostol. In the early pregnancy group (first 10 weeks) there was overwhelming evidence that misoprostol was associated with a favourable outcome. In the late pregnancy group (11 - 12 completed weeks) the difference was not statistically significant. This was supported by the finding that misoprostol also had no effect on 'ease' and duration of the procedure after 10 weeks of gestation (Table III).

Discussion

This randomised controlled trial using 600 μg vaginal misoprostol self-administered 2 - 4 hours pre-operatively showed satisfactory cervical dilatation in a significantly larger proportion of women in the first trimester of pregnancy in the treatment group. This resulted in a procedure that was shorter and more likely to be regarded as 'easy' by the operators, and that had fewer treatment failures.

This is the first randomised controlled trial to show the effectiveness of vaginal misoprostol administered shortly before the operative procedure in cases drawn from throughout the first trimester. The alternative 12-hour pre-operative regimen[4] required that women either had to be admitted overnight, or had to take the medication themselves at home. In South Africa imperatives of cost minimisation usually require abortions to be undertaken as day cases. Some institutions are reluctant to give women the tablets to take off-site in case they do not return for the vacuum aspiration or develop heavy bleeding during the night when access to medical care may be difficult. Exposure to misoprostol *in utero* in dosages as low as 200 μg has been associated with congenital deformities at birth,[12] and bleeding is commonly reported after misoprostol administration,[6,13] as was also found in this study. Now that the effectiveness of moistened tablets administered as little as 2 hours pre-operatively has been demonstrated, the additional risks associated with the practice of giving women tablets off-site can no longer be justified.

This is also the first trial to evaluate self-administered vaginal misoprostol. This method was developed as nationwide 'value clarification' workshops for health care workers held before implementation of the new Act had indicated that care providers were more willing to assist women with surgical completion of an induced abortion than to initiate an abortion (E T M de Jonge – unpublished data). Self-insertion of the tablets was compatible with a low-technology approach to the procedure. Although women did not report any difficulty in inserting the tablets, it is not known to what extent the outcome measures were influenced by electing this pragmatic approach. We suspect that the outcome would have been at least as good if not superior if misoprostol

Table III. Secondary outcomes

	Misoprostol	Placebo	*P*-value
All cases			
Length of procedure in seconds			
Median (IQR)	180.0 (135 - 285)	249 (180 - 352.5)	
Mean (SD)	219.9 (118.4)	320.6 (277.2)	0.0013*
Gestation < 69 days			
Length of procedure in seconds			
Median (IQR)	170.5 (131 - 232)	222.5 (180 - 332)	
Mean (SD)	190.1 (89.1)	282.0 (202.3)	0.0001*
Gestation ≥ 70 days			
Length of procedure in seconds			
Median (IQR)	296 (200 - 397)	299 (209 - 443)	
Mean (SD)	311.1 (148.7)	441.4 (418.0)	0.116*
All cases			
Ease of procedure			
Easy	108 (81.8%)	88 (63.3%)	0.0082†
Normal	11 (8.3%)	24 (17.3%)	
Difficult	6 (4.6%)	11 (7.9%)	
Impossible	7 (5.3%)	16 (11.5%)	
Gestation < 69 days			
Ease of procedure			
Easy	85 (85%)	69 (63.3%)	0.005†
Normal	6 (6%)	17 (15.6%)	
Difficult	3 (3%)	7 (6.4%)	
Impossible	6 (5%)	16 (14.7%)	
Gestation ≥ 70 days			
Ease of procedure			0.695†
Easy	23 (71.9%)	19 (63.3%)	
Normal	5 (15.6%)	7 (23.3%)	
Difficult	3 (9.4%)	4 (13.3%)	
Impossible	1 (3.1%)	0	

* Unequal variance *t*-test.
† Fisher's exact test.

Table IV. Side-effects

	Misoprostol		Placebo		
Side-effects	*N*	%	*N*	%	*P*-value
Pre-operative pain					
Present	83	65.4	53	40.2	< 0.001*
Absent	44	34.6	79	59.8	
Pre-operative nausea/vomiting					
Present	24	19.2	26	19.7	0.92*
Absent	101	80.8	106	80.3	
Peri-operative pain					
Very severe	6	4.5	3	2.2	0.059†
Severe	14	10.5	17	12.4	
Moderate	25	18.8	14	10.2	
Mild	62	46.6	59	43.1	
None	26	19.6	44	32.1	

* χ^2.
† Armitage's χ^2 for trend.[16]

had been inserted in the posterior fornix of the vagina under direct speculum inspection by a care provider.

We opted for a dose of 600 μg misoprostol as a study by Singh *et al.*[13] had shown that this was the lowest dose to result in adequate cervical dilatation in all cases, although the side-effects were more prevalent than in the 200 and 400 μg groups.[13] We found that the side-effects of 600 μg vaginal misoprostol were of minimal intensity, with gastro-intestinal symptoms similar to those in the placebo group. There was more peri-operative pain reported in the misoprostol group. No major adverse events were reported during the trial, confirming that first-trimester TOP by suction curettage is inherently a safe procedure. It also shows that the procedure can be performed safely by appropriately trained midwives.

In subgroup analysis by gestational age group, we found that from 10 weeks of gestation misoprostol provided no additional cervical priming effect over what we consider to be a physiological process of cervical softening as pregnancy progresses. This finding is in keeping with the finding of el-Rafaey *et al.*[10] However, the study was not designed to test this qualified use of misoprostol in the first trimester. The hypothesis that misoprostol has no additional effect on cervical dilatation after 10 weeks of gestation needs further study. However, we acknowledge that if these results are confirmed, separation of these two gestational age groups will be extremely difficult programmatically, the more so as ultrasound is seldom available in this setting.

The low success rate of repeated misoprostol (1 out of 7) is a phenomenon well known to clinicians involved in abortion care. As prostaglandins act mainly on the cervical connective tissue,[10] misoprostol resistance is most likely the result of previous cervical scarring. In the 6 women who were taken to theatre for a dilatation under anaesthesia, 5 were found to have stenotic cervices, difficult to dilate even with forced dilatation. We do not, therefore, recommend repeated misoprostol administration for cervical priming.

Research on cervical priming using misoprostol has employed a variety of outcome measures. Some authors have used baseline cervical dilatation as a continuous variable, while others have used the cumulative force needed to dilate the cervix (measured by a cervical tonometer)[10] as an objective measure of the ease of the procedure. In this study the decision to use a binary outcome based on a notion of 'satisfactory' dilatation for the procedure was based on examination of a local case series (M Bennun — personal communication), which showed the distribution of cervical dilatation to be clustered around even-numbered Hegar dilators. This was discussed at an abortion research meeting involving senior South African gynaecologists, and the view was expressed that a baseline dilatation of 6 or below was normally indicative of a difficult or impossible procedure under non-opioid analgesia. The results of the operators' assessment of ease of procedure support the conclusions of this study based on the primary outcome, but indicate that a smaller baseline cervical dilatation does not necessarily predict a difficult procedure. When one compares Tables II and III, it can be seen that there is a discrepancy between the proportion of unsatisfactory cervical dilatations, and procedures rated as 'difficult' and 'impossible'.

Recently a 95% complete abortion rate was reported in women requesting TOP at 9 - 13 weeks of gestation using mifepristone and higher dosages of vaginal misoprostol.[14] The side-effect profile was substantial, with 70% of women requiring analgesia. The short median induction to abortion interval of 4.33 hours in this study warrants comparison with primary surgical curettage as a day procedure in terms of cost-effectiveness, safety and consumer acceptance.

We conclude that a single dose of self-administered vaginal misoprostol is effective for cervical priming before surgical suction TOP. Given that it is effective when self-administered 2 - 4 hours pre-operatively, any possible risk associated with its use off-site cannot be justified. Further research is needed to evaluate its qualified use in the first 9 weeks of pregnancy. Women's preferences as regards the method of application (self-administration versus administration by a care provider), route of administration and the impact on efficacy also need further research. Besides avoiding the effects of forceful dilatation on later reproductive performance,[10,15] cervical priming with misoprostol proved of particular value in settings where abortion care is offered by trained midwives, and in areas with less developed health services where women have to travel long distances to get access to abortion care and cannot afford return visits for a failed attempt.

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