Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial

Lancet 2007; 369: 1938–46

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Summary

Background The most effective route and best interval between several doses of misoprostol to induce abortion have not been defined. Our aim was to assess the effects of the interval between multiple doses of misoprostol and the route of administration to terminate pregnancy.

Methods 2066 healthy pregnant women requesting medical abortion with 63 days or less of gestation were randomly assigned within 11 gynaecological centres in six countries to the four treatment groups (three doses of 0·8 mg misoprostol given sublingually at 3-h intervals, vaginally 3 h, sublingually 12 h, and vaginally 12 h), stratifying by gestational age. This was an equivalence trial with a 5% margin of equivalence. The primary endpoints were efficacy of treatment to achieve complete abortion and to terminate pregnancy. The main efficacy analysis excluded women lost to follow-up. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN10531821.

Findings Efficacy outcomes were analysed for 2046 women (99%), excluding 20 lost to follow-up. Complete abortion rates at 2-week follow-up were recorded for 431 (84%) in the sublingual and for 434 (85%) women in the vaginal group when misoprostol was given at 3-h intervals (difference 0·4%, 95% CI –4·0 to 4·9, p=0·85 equivalence shown), and for 399 (78%) in the sublingual and for 425 (83%) in the vaginal 12-h groups (4·6%, –0·2 to 9·5, p=0·06, equivalence not shown). In the 3-h groups, pregnancy continued in 29 (6%) women after sublingual and in 20 (4%) women after vaginal administration (difference 1·8%, 95% CI –0·8 to 4·4, p=0·19, equivalence shown); in the 12-h groups it continued in 47 (9%) after sublingual and in 25 (5%) after vaginal administration (4·4%, 1·2–7·5, p=0·01, vaginal better than sublingual). Differences for complete abortion between intervals for sublingual and vaginal routes were 6% (95% CI 1·0–10·6, p=0·02, 3 h better than 12 h) and 2% (–2·9 to 6·1, p=0·49, equivalence not shown), respectively; for continuing pregnancies they were 4% (0·4–6·8, p=0·03, 3 h better than 12 h) and 1% (–1·5 to 3·5, p=0·44, equivalence shown), respectively.

Interpretation Administration interval can be chosen between 3 h and 12 h when misoprostol is given vaginally. If administration is sublingual, the intervals between misoprostol doses need to be short, but side-effects are then increased. With 12-h intervals, vaginal route should be used, whereas with 3-h intervals either route could be chosen.

Introduction

Vacuum aspiration for termination of early pregnancy is one of the safest procedures when done by a trained provider. However, developing countries do not usually have enough trained staff and cannot provide safe abortion services. Provision of non-surgical abortion could improve the situation in such settings. Furthermore, women should be provided with a choice of methods if they wish to avoid invasive procedures.[1]

The medical abortion regimen of mifepristone followed by a suitable prostaglandin analogue, most commonly misoprostol, is available in over 30 countries for termination of early pregnancy. For countries in which mifepristone has not been available, various misoprostol only regimens are used, but there is no evidence about the most effective route of administration or interval between multiple doses of the drug.

The effects of misoprostol on the uterine cervix and contractility are crucial for successful abortion. About 3 h after misoprostol is given the cervix has softened and dilated sufficiently to perform vacuum aspiration,[2] and this effect occurs whichever route of administration is used. However, regular contractions might fail to develop after oral administration of misoprostol,[3,4] which could be why complete abortion rates are very low when the drug is given orally.[4,5] After vaginal administration, however, the strength of contractility continues to increase at least for 4 h.[3] When misoprostol is taken sublingually, uterine contractions, which are initially stronger than are contractions after vaginal administration, start diminishing about 2–3 h after administration.[6]

Despite insufficient large studies comparing efficacy of misoprostol alone to induce abortion, several reports clearly show that vaginal administration of misoprostol is

more effective than is oral administration.[4,5,7] Since the vaginal route is not desirable in some settings, sublingual use of misoprostol has been proposed, and the efficacy and acceptability data from a pilot study seem promising.[8] However the drug is given, experience suggests that several high doses of misoprostol are necessary to induce abortion, and most researchers have used three doses of 0·8 mg.[7–10] Most investigators report fairly long administration intervals, even 48 h,[9] although 3-h intervals have also been tested. A group of clinicians and researchers recommended a regimen of 0·8 mg vaginally repeated after 24 h,[11] although some providers and women have indicated that lengthy intervals between doses are less acceptable than are short intervals because the procedure takes too long and they prefer treatment to finish within 1 day.[9]

The effectiveness of vaginal administration is well known, but if women prefer to take the drug orally, sublingual administration of tablets could be an option if the efficacy is equivalent. Thus, we undertook a randomised equivalence trial of two intervals between misoprostol doses and two routes of administration in termination of pregnancies for women with gestational age of 63 days or less.

Methods

Patients

Our trial was done in 11 obstetrics and gynaecology departments in teaching hospitals in Yerevan, Armenia; Havana, Cuba; Tbilisi, Georgia; Mumbai, New Delhi, and Trivandrum, India; Ulaanbaatar, Mongolia; and Hanoi and Ho Chi Minh City, Vietnam. Institutional review boards at all participating hospitals and the WHO Secretariat Committee on Research on Human Subjects gave ethics approval.

Women requesting early termination of pregnancy were provided with information about the study, screened for eligibility if willing to participate by clinic personnel, and included if they were healthy, older than the age of legal consent, had haemoglobin concentration 95 g/L or more, had single intrauterine pregnancy with duration of 63 days or less verified by ultrasound, agreed to return for one or more follow-up visits, and accepted surgical termination of pregnancy should the treatment fail.

We excluded women who had any indication of serious past or present illness; those allergic to misoprostol or with a strong allergic tendency in general; heavy smokers (>20 cigarettes a day); those with a scar in the uterus or cervix or any gynaecological anomaly detected with ultrasound; a history or evidence of mitral stenosis, glaucoma, or sickle cell anaemia; diastolic blood pressure greater than 90 mm Hg; uncontrolled bronchial asthma; systolic blood pressure less than 90 mm Hg; history or evidence of thromboembolism or liver disease; presence of an intrauterine device in utero; or haemolytic disorders.

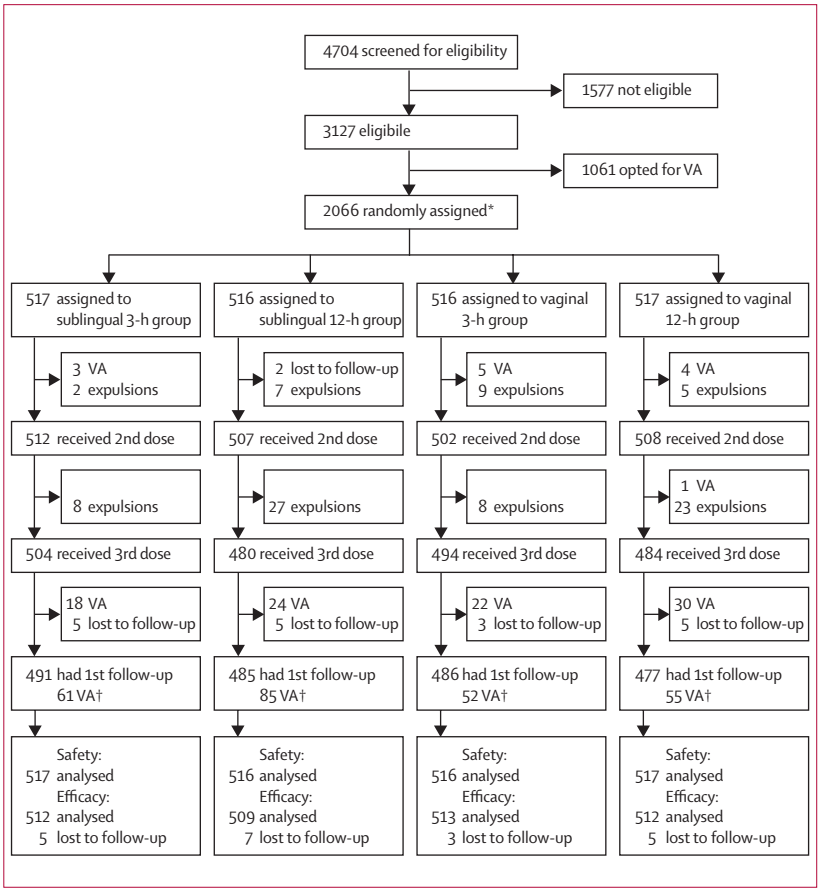

Figure 1: **Trial profile**
*All received first dose. †VA at first follow-up or later. VA=vacuum aspiration or dilatation and curettage.

	Sublingual 3 h (n=517)	Sublingual 12 h (n=516)	Vaginal 3 h (n=516)	Vaginal 12 h (n=517)
Demographic and physical				
Age (years)	26·7 (5·8)	26·7 (5·8)	26·5 (5·7)	26·6 (5·4)
Weight (kg)	53·2 (10·0)	53·2 (9·7)	52·7 (9·4)	53·3 (9·9)
Haemoglobin (g/L)	119·2 (11·4)	118·7 (11·7)	119·7 (11·5)	120·0 (12·2)
Ethnic group				
Chinese	47 (9%)	47 (9%)	47 (9%)	47 (9%)
Non-Chinese Asian or black	318 (62%)	313 (61%)	307 (60%)	320 (62%)
White	152 (29%)	156 (30%)	162 (31%)	150 (29%)
Obstetric and gynaecological history				
Nulliparity	223 (43%)	200 (39%)	213 (41%)	207 (40%)
Previous abortion	184 (36%)	185 (36%)	188 (36%)	196 (38%)
Gestational age* (days)				
29–49	245 (47%)	246 (48%)	249 (48%)	239 (46%)
50–56	144 (28%)	146 (28%)	137 (27%)	151 (29%)
57–63	128 (25%)	124 (24%)	130 (25%)	126 (24%)
Median (IQR)	50 (43–56)	50 (43–56)	50 (43–57)	50 (43–56)

Data are number (%) or mean (SD), unless otherwise indicated. *Gestational age assessed by ultrasound (one woman in the vaginal 12-h group had no ultrasound examination at admission).

Table 1: **Baseline characteristics for all women enrolled**

	Outcome					
	Complete abortion	Failure of complete abortion				
		Total	Incomplete abortion	Missed abortion	Continuing pregnancy	Undetermined†
Sublingual 3 h (n=512)	431(84%;80·7–87·2)	81 (16%; 18·1–25·4)	28 (6%; 3·7–7·8)	14 (3%; 1·5–4·5)	29 (6%; 3·8–8·0)	10 (2%; 0·9–3·6)
Sublingual 12 h (n=509)	399(78%;74·6–81·9)	110 (22%; 18·1–25·4)	31 (6%; 4·2–8·5)	26 (5%; 3·4–7·4·)	47 (9%; 6·9–12·1)	6 (1%; 0·4–2·5)
Vaginal 3 h (n=513)	434(85%;81·2–87·6)	79 (15%; 12·4–18·8)	27 (5%; 3·5–7·6)	17 (3%; 1·9–5·3·)	20 (4%; 2·4–6·0)	15 (3%; 1·6–4·8)
Vaginal 12 h (n=512)	425(83%;79·5–86·2)	87 (17%; 13·8–20·5)	21 (4%; 2·6–6·2)	26 (5%; 3·3–7·4)	25 (5%; 3·2–7·1)	15 (3%; 1·6–4·8)
Total (n=2046)	1689 (83%)	357 (17%)	107 (5%)	83 (4%)	121 (6%)	46 (2%)

Data are number (%; 95% CI) or number (%). *Women lost to follow-up excluded. †Women had vacuum aspiration before the outcome of medical abortion could be assessed.

Table 2: **Outcomes of treatment by treatment group***

All participants provided written informed consent before enrolment. Medical, gynaecological, and obstetric histories were recorded and bacteriological tests and Rhesus typing done according to the routine of the centre.

Study design

On the basis of uterine contractility studies and the finding that contractility seems to start to decline 2–3 h after sublingual administration, we chose 3 h as the short interval. As the long interval we chose 12 h because contractility is unlikely to continue beyond this time after vaginal administration. Interventions included three doses of 0·8 mg misoprostol. We used a computer-generated randomisation sequence to assign 192 participants within every centre to one of the four following route-interval combinations: sublingual 3 h, vaginal 3 h, sublingual 12 h, and vaginal 12 h.

Every centre received assignments by randomly permuted blocks with a fixed block size of eight. Randomisation was stratified by centre and gestational age. Allocation was concealed with sealed, sequentially numbered envelopes, which were filled and labelled in accordance with the list of randomisation for each centre by Magistra (Geneva, Switzerland). Every dose consisted of four sublingual tablets (active or placebo) and four vaginal tablets (active or placebo) used at the same time. Placebo tablets were of similar shape and colour to misoprostol (Cytotec, Searle, UK) tablets but differed by taste and were without the name of the manufacturer. Thus, the route of administration and interval were known.

We aimed to show that short (3 h) and long (12 h) intervals between misoprostol doses were equivalent and that the sublingual and the vaginal route of administration were equivalent with respect to the efficacy in achieving complete abortion or terminating pregnancy, within a margin of 5%.

To establish the equivalent efficacy of the 3-h and 12-h regimens or the equivalent efficacy of the two routes of administration, we assumed no interaction of interval by route. We needed the 95% CI for the difference in complete abortion rates to be within the margin of equivalence of 5%, with a probability of 80%. If complete abortion rates by the two routes (or by the two intervals) were both equal to 86%, about 1000 patients would be needed in each route (or in each interval), or 500 in each of the four groups—ie, a total of about 2000 women for the whole study. Allowing for 5% of undetermined outcomes or loss to follow-up, 2100 women would need to be recruited. Recruitment started in June, 2002, and continued until May, 2004.

The primary outcome measure was efficacy of the treatment in inducing abortion. Complete abortion was defined as passing of the products of conception without needing vacuum aspiration or dilatation or curettage during the follow-up period; incomplete abortion as expulsion of fetus but some products of conception remaining in uterus, needing evacuation; missed abortion as gestational sac in uterus without cardiac activity on ultrasound examination, needing emptying of uterus; continuing pregnancy as growing gestational sac with fetal heart activity; and undetermined as women who had surgical treatment before the treatment effect could be assessed. Efficacy was assessed at the follow-up visit 2 weeks after the start of treatment.

Other outcome measures were side-effects recorded 1 h and 3 h after every administration of misoprostol at the clinic and daily by women after the treatment, until the

	RR (95% CI)	Difference (95% CI)	p value
Comparison of administration routes*			
Failure to terminate pregnancy			
Sublingual 12 h *vs* vaginal 12 h	2·0 (1·2–3·3)	4·4% (1·2–7·5)	0·01
Sublingual 3 h *vs* vaginal 3 h	1·5 (0·8–2·7)	1·8% (–0·8–4·4)	0·19
Failure to achieve complete abortion			
Sublingual 12 h *vs* vaginal 12 h	1·3 (1·0–1·8)	4·6% (–0·2–9·5)	0·06
Sublingual 3 h *vs* vaginal 3 h	1·0 (0·7–1·4)	0·4% (–4·0–4·9)	0·85
Comparison of intervals*			
Failure to terminate pregnancy			
Sublingual 12 h *vs* sublingual 3 h	1·7 (1·1–2·7)	3·6% (0·4–6·8)	0·03
Vaginal 12 h *vs* vaginal 3 h	1·3 (0·7–2·3)	1·0% (–1·5–3·5)	0·44
Failure to achieve complete abortion			
Sublingual 12 h *vs* sublingual 3 h	1·5 (1·1–2·0)	5·8% (1·0–10·6)	0·02
Vaginal 12 h *vs* vaginal 3 h	1·1 (0·8–1·6)	1·6% (–2·9–6·1)	0·49

RR=relative risk. *Second group in each comparison is reference group. †Women lost to follow-up excluded.

Table 3: **Relative risk of failure to achieve complete abortion and failure to terminate pregnancy†**

first follow-up visit. Side-effects were classified as pregnancy related, treatment related, and those related to the abortion process itself.

Procedures

The first dose of treatment was given at the clinic to all women, after which they were observed for 3 h. Vaginal tablets were wetted with a few drops of water just before administration. Women were advised to take all three doses. Women had the choice of self-administering the second dose at home in the 12-h groups and the third dose in the 3-h groups. They attended hospital the following morning for preliminary assessment of the outcome and for administration of the third dose in the 12-h groups. They were asked to keep a diary about side-effects and bleeding until the follow-up visit. No incentives were given, and the trial drugs were supplied free of charge to participants.

A follow-up visit was scheduled 2 weeks after treatment, during which the diary card was reviewed, haemoglobin measured, and pelvic examination done. If the clinical findings were compatible with complete abortion, no further action was needed, otherwise ultrasound examination was done. Vacuum aspiration was undertaken if women had an incomplete abortion, a missed abortion, or a continuing pregnancy. For women with incomplete abortion, the aspirate was sent for histological examination to confirm the diagnosis. Further follow-up visits were arranged if needed.

Principal investigators met before the trial to review the protocol and ensure uniform criteria for assessment of the outcomes. During the study, the trial coordinator and other WHO staff visited trial sites. Data-quality monitoring was done in accordance with the standard operating procedures used in the Department of Reproductive Health and Research, WHO, Geneva.

Statistical analysis

Data were analysed centrally at WHO with the statistical software STATA (version 8.0). An independent data and

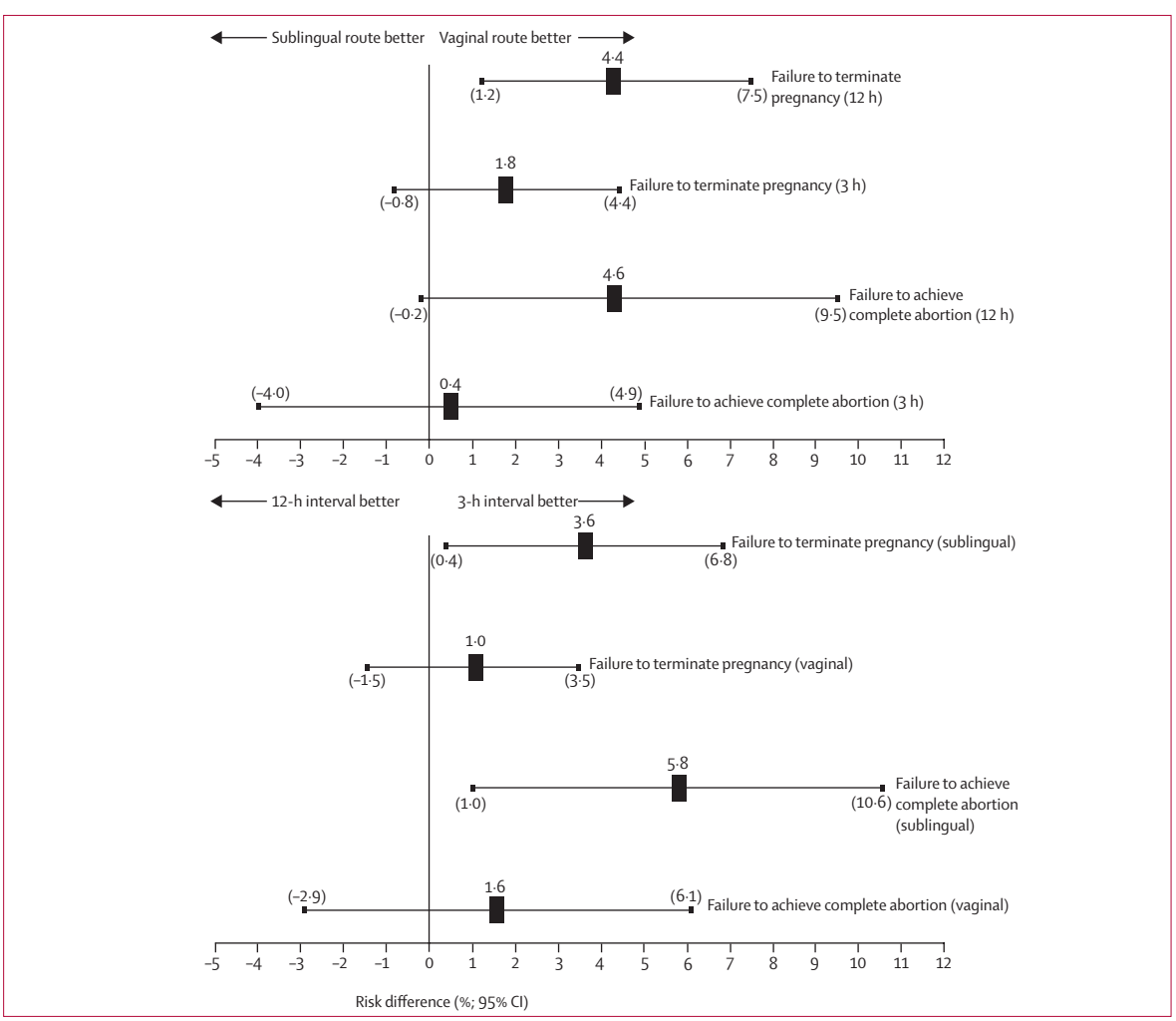

Figure 2: **Percentage difference and 95% CI in relative risk of failure to achieve complete abortion and failure to terminate pregnancy according to route of administration (upper) and interval between doses (lower)**

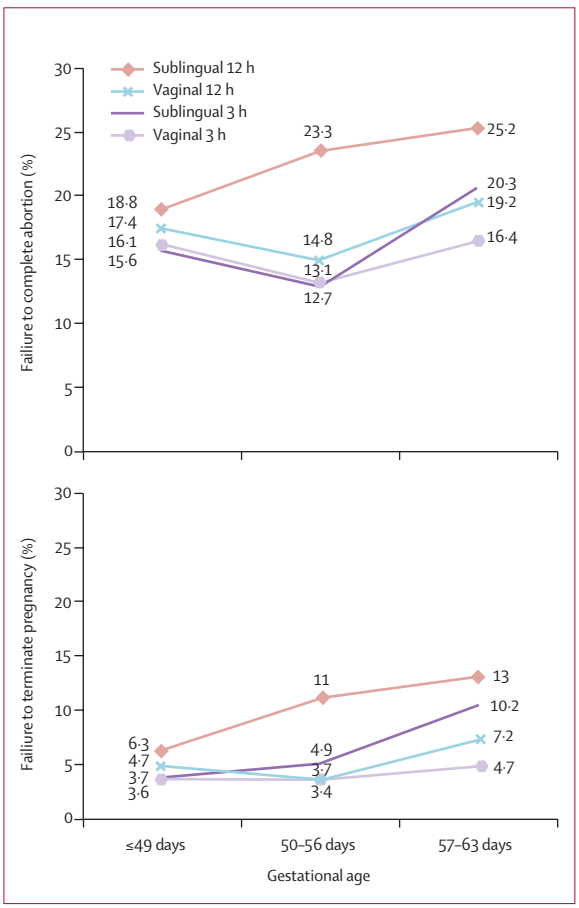

Figure 3: **Efficacy of misoprostol regimens by gestational age for failure to complete abortion (upper) and failure to terminate pregnancy (lower)**

safety monitoring board discussed the results of two interim analyses and looked at the stopping rules stated in the protocol. A regimen was discontinued if the lower 95% confidence limit for the failure rate for complete abortion was above 30% or above 10% for the live pregnancy rate. We did not have pre-specified stopping rules based on showing equivalence or superiority of a regimen before the trial ended.

In our main analysis for efficacy, we prespecified exclusion of women for whom the outcome of treatment was unknown, unlike other WHO previous trials[12,13] in which women with unknown outcomes (lost to follow-up) were included in the main analysis as failures. Furthermore, we did two per-protocol analyses for efficacy, one in which we excluded undetermined cases, in addition to women lost to follow-up, and the other excluding also women with compliance or eligibility criteria violations. Percentages of women with complete abortion, incomplete abortion, missed abortion, continuing live pregnancy, and undetermined outcome were calculated. For the safety analysis, we included all women receiving at least one dose of misoprostol and for whom there was safety information.

We compared routes of administration for each interval and intervals for each route. For these comparisons, relative risks (RR) of failure to achieve a complete abortion and failure to terminate pregnancy and the two-sided 95% CIs were calculated by standard methods, as well as risk differences and two-sided 95% CIs, which were used to test the equivalence hypotheses.[14] We analysed continuing pregnancies with the same criterion and margin. Logistic regression and odds ratios were used to assess the effect of the route, the interval, and their interaction on efficacy, and also to adjust for and assess the effect of age, ethnic group, parity, and gestational length. A stratified efficacy analysis was done by gestational age. Percentages of women with each side-effect were calculated, and the effect of parity on side-effects was investigated. All analyses had been specified a priori.

This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN10531821.

Role of the funding source

The donors and sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. The most common reasons for non-eligibility (some women had more than one reason) were unwillingness to return for follow-up visits (634; 40%), gestational age greater than 63 days (539; 34%), and scar in uterus or cervix (352; 22%). Other reasons included health problems (263; 17%), gynaecological abnormality (166; 11%), and failure to consent to vacuum aspiration in case of treatment failure (66; 4%). Since 1061 eligible women opted for vacuum aspiration, the remainder of women were enrolled and randomly assigned to the four groups.

Table 1 shows baseline characteristics. The mean age of women was about 27 years, most were Asian (about 70%), and 40% were nulliparous. The 20 women lost to follow-up were younger (average of 24 years old) than were those who completed treatment and they were mainly Asian (90%).

All 2066 women received the first dose at the clinic, 2029 (98%) received the second dose (in the clinic or at home), and 1962 (95%) had all three doses of the drug. 20 (1%) women were lost to follow-up during the trial (figure 1). Of 107 women having vacuum aspiration before the 2-week follow-up, 46 were thought to have undetermined outcome of treatment since they discontinued with the trial before the outcome could be assessed (figure 1). During the whole study period there were 360 (17%) vacuum aspirations. The most common reasons were continuing pregnancy (n=120; 33%),

incomplete abortion (105; 29%), missed abortion (83; 23%), woman's choice (25; 7%), medical indication (23; 6%), or other reason (four; 1%).

The efficacy of the treatment was assessed, as stated in the protocol, 2 weeks after treatment. Efficacy outcomes were analysed for 2046 women (99%), including 46 women with undetermined outcome. Table 2 shows patient outcome by treatment group. We tested the interaction of route by interval for the binary outcomes, and failure of complete abortion and continuing live pregnancy were not significant (p=0·22 and p=0·23, respectively). However, since this test did not have sufficient power (we had assumed no interaction for the sample size calculation) and interaction in the point estimates was noted, we compared intervals within each route and routes within each interval (table 3, and figures 2 and 3).

Complete abortion rates at 2-week follow-up proved equivalent in the sublingual and vaginal groups when misoprostol was given at 3-h intervals (tables 2 and 3). Complete abortion rates were higher in the vaginal group than in the sublingual group when intervals were 12 h and equivalence was not shown (tables 2 and 3). In the 3-h groups, the number of pregnancies continued after sublingual and vaginal administration proved equivalent; in the 12-h groups pregnancy continued in fewer women after vaginal than after sublingual administration, and vaginal administration proved better than sublingual administration (p=0·01; tables 2 and 3). For complete abortion between intervals for sublingual administration, the 3-h regimen was more effective than the 12-h regimen (p=0·02), but the difference between intervals with vaginal administration failed to show equivalence. For continuing pregnancies, the 3-h interval was better than the 12-h interval for the sublingual route, and equivalence was shown between intervals in the vaginal administration group. Adjustment for centre and baseline variables (age, ethnic group, parity, and gestational age) with logistic regression showed almost identical results (data not shown).

When the 46 women with undetermined outcomes, as well as the 20 women lost to follow-up, were excluded from the analysis, results were much the same in trend but there were changes in significance for outcome failure of complete abortion in the comparison of routes (difference at 3-h intervals: 1%, 95% CI –2·9 to 5·5, equivalence not shown; difference at 12-h intervals: 6%, 1·5–10·9, vaginal better than sublingual). Almost identical results were obtained when a further 31 women with protocol violations were excluded (51/2066, 3%; data not shown). The protocol violations consisted of one woman who did not have ultrasound examination at admission, one who stopped treatment after the second dose and then had a missed abortion, and 29 who did not receive doses at intervals according to the protocol.

	Sublingual 3 h (n=517)	Sublingual 12 h (n=516)	Vaginal 3 h (n=516)	Vaginal 12 h (n=517)	p value*
Pregnancy-related symptoms					
Nausea					
Before treatment	95 (18%)	110 (21%)	94 (18%)	115 (22%)	-
After first dose	140 (27%)	139 (27%)	122 (24%)	146 (28%)	0·34
After second dose	135 (26%)	95 (19%)	108 (22%)	81 (16%)	0·0006
After third dose‡	78 (16%)	50 (10%)	64 (13%)	47 (10%)	0·02
Vomiting					
Before treatment	24 (5%)	20 (4%)	23 (5%)	24 (5%)	-
After first dose	55 (11%)	45 (9%)	32 (6%)	33 (6%)	0·03
After second dose†	46 (9%)	22 (4%)	28 (6%)	12 (2%)	<0·0001
After third dose‡	29 (6%)	11 (2%)	11 (2%)	4 (1%)	<0·0001
Side-effects related to abortion process					
Lower abdominal pain					
Before treatment	38 (7%)	31 (6%)	33 (6%)	32 (6%)	-
After first dose	413 (80%)	409 (79%)	409 (79%)	414 (80%)	0·98
After second dose†	461 (90%)	403 (80%)	445 (89%)	400 (79%)	<0·0001
After third dose†	437 (87%)	328 (68%)	429 (87%)	353 (73%)	<0·0001
Diarrhoea					
Before treatment	9 (2%)	2 (<1%)	3 (1%)	4 (1%)	-
After first dose	191 (37%)	177 (34%)	119 (23%)	118 (23%)	<0·0001
After second dose†	228 (45%)	172 (34%)	147 (29%)	106 (21%)	<0·0001
After third dose‡	195 (39%)	114 (24%)	113 (23%)	66 (14%)	<0·0001
Fever					
Before treatment	0	1 (<1%)	1 (<1%)	1 (<1%)	-
After first dose	46 (9%)	39 (8%)	34 (7%)	28 (5%)	0·16
After second dose†	100 (20%)	28 (6%)	78 (16%)	14 (3%)	<0·0001
After third dose‡	73 (15%)	11 (2%)	65 (13%)	5 (1%)	<0·0001
Chills/shivering					
Before treatment	4 (1%)	6 (1%)	4 (1%)	5 (1%)	-
After first dose	237 (46%)	214 (42%)	186 (36%)	166 (32%)	<0·0001
After second dose†	217 (42%)	178 (35%)	183 (37%)	118 (23%)	<0·0001
After third dose‡	175 (35%)	131 (27%)	142 (29%)	72 (15%)	<0·0001
Headache					
Before treatment	20 (4%)	20 (4%)	27 (5%)	17 (3%)	-
After first dose	47 (9%)	49 (10%)	44 (9%)	44 (9%)	0·93
After second dose†	65 (13%)	40 (8%)	58 (12%)	41 (8%)	0·02
After third dose‡	48 (10%)	29 (6%)	47 (10%)	32 (7%)	0·07

Data are number (%). *With Banferroni correction for multiple inferences, a difference is significant at 5% if p<0·002. †After second dose: n=512 for sublingual 3 h, n=507 for sublingual 12 h, n=502 for vaginal 3 h, and n=508 for vaginal 12 h. ‡After third dose: n=504 for sublingual 3 h, n=480 for sublingual 12 h, n=494 for vaginal 3 h, and n=484 for vaginal 12 h.

Table 4: **Women with pregnancy-related symptoms and side-effects related to the abortion process, listed by group at different timings**

Women whose length of pregnancy was between 57 days and 63 days had a significantly higher risk of failure to terminate pregnancy than did those whose pregnancy was 49 days or less (RR=2·0, 95% CI 1·3–3·1; absolute risk=4·2, 1·4–7·0). The risk of failure to achieve complete abortion was higher for women whose length of pregnancy was between 57 days and 63 days than for those whose pregnancy was 49 days or less (RR=1·2, 0·9–1·6; absolute risk=3·3, –1·0 to 7·5), although this result was not significant.

The interaction of gestational age by treatment group was not significant (p=0·19). However, since the trial was not powered to detect this interaction, we did a stratified analysis of efficacy by gestational age. The results do not suggest a qualitative interaction (ie, treatment effects do not change sign substantially with gestational age group), but the difference in efficacy seems to rise with an increase in gestational age (figure 3).

In 1796 women with complete and incomplete abortion outcomes, timing of expulsion, assessed for 1407 (78%) women, differed significantly between treatment groups (p<0·0001). In the vaginal 3-h and 12-h groups, the median time was 7·7 h (IQR 6·0–11·0) and 12·2 h (7·0–26·0), respectively, and in the sublingual 3-h and 12-h groups, 7·5 h (5·8–11·0) and 11·3 h (6·4–24·5), respectively. The timing of expulsion was virtually the same for women with gestational age 49 days or less, 50–56 days, and 57–63 days: 9·1 h (6·3–17·7), 8·9 h (6·0–17·1), and 8·2 h (5·9–13·3), respectively; p=0·20. In the 3-h groups, 6% (44/718) of women aborted between first and second dose, whereas 50% (345/689) did so in the 12-h groups; between second and third dose, 26% (186/718) and 22% (151/689), respectively, of women aborted.

Pregnancy-related symptoms, such as nausea and vomiting, increased after the first dose compared with the baseline value before treatment, but their frequency decreased as treatment advanced (table 4). Pain was the most frequent side-effect. The frequency and intensity (scale 0–10) increased after the second dose when misoprostol was given at 3-h intervals (p<0·0001). There was no difference in the amount of pain reported between routes. Nulliparous women reported pain more frequently than did parous women (743 [88%] *vs* 901 [74%], p<0·0001 after first dose; 761 [93%] *vs* 948 [79%], p<0·0001 after second dose; 700 [90%] *vs* 847 [72%], p<0·0001 after third dose, respectively).

Chills and shivering were common during treatment, with more than 40% of women reporting them after sublingual administration (table 4). Fever (temperature >38° C) after the second dose, was more common when the drug was given at 3-h intervals than at 12-h intervals. Diarrhoea was reported most frequently by women after sublingual administration than after vaginal administration, especially at 3-h intervals.

A total of 154 (8%) women came to unscheduled visits (with one or more complaints); 83 (54%) with vaginal bleeding, 56 (36%) with lower abdominal pain, 27 (18%) with nausea, and 19 (12%) with vomiting. Symptoms of diarrhoea and fever accounted for five (3%) and seven (5%), respectively, of the unscheduled visits. Seven women (<1%) with heavy or persistent bleeding after treatment were given blood transfusions or plasma expander. Overall, 13 (1%) women were admitted—six for treatment or supervision of signs and symptoms related to the treatment, and seven for surgical intervention because of treatment failure. They stayed in hospital for 12–72 h (median 24 h). A total of 27 women were treated for vaginal infection before misoprostol was given. After misoprostol treatment, three women had signs of pelvic inflammatory disease during follow-up, two of them after surgical intervention. Two women had an allergic reaction after the first dose of misoprostol, showing symptoms of erythematous rashes, itching in hands and feet, and general chills, which disappeared after 3 h.

Mean duration of bleeding was 11·5 days (SD=5·9; much the same in all groups), and the interval between treatment and first menses was 34·9 days (SD=7·4; much the same in all groups).

Discussion

Our findings show that misoprostol can be used either vaginally or sublingually for termination of early pregnancy. When vaginal administration is used, the intervals between misoprostol doses can range from 3 h to 12 h without significantly affecting efficacy. However, if misoprostol is given sublingually, 3-h intervals between multiple doses are more effective than are 12-h intervals, but at the cost of higher rates of side-effects.

When prostaglandin analogues were tested for pregnancy termination some 30 years ago, gastrointestinal side-effects and lower abdominal pain were usually severe, restricting the usefulness of the compounds that were available at that time.[15] With mifepristone pretreatment, which sensitises the uterus to prostaglandins, small doses of prostaglandins are sufficient to induce abortion and, consequently, the rate of side-effects is reduced. However, limited access to mifepristone and wide availability of misoprostol has encouraged providers and women to start using various misoprostol only regimens for pregnancy termination.

Our randomised trial investigated the effects of the interval between multiple doses of misoprostol and the route of administration of misoprostol efficacy to terminate pregnancy. Although there was no group with mifepristone pretreatment, our results suggest that the efficacy of the four regimens is less than that reported after mifepristone-misoprostol regimen—pregnancies continued in 4%–9% of women in our trial, whereas the continuing pregnancy rate after mifepristone followed by a single vaginal dose of 0·8 mg misoprostol is less than 1%[12,16] in pregnancies of up to 9 weeks' gestation.

The assumption of no interaction between route and interval used for design of the trial to test the hypothesis of equivalence resulted in low power of comparisons of routes within each interval and of intervals within each route. Despite this limitation, equivalence between routes with a 3-h interval was noted for both outcomes, and between intervals when the vaginal route is used, for failure to terminate pregnancy.

Carbonell and co-workers' study[7] showed that vaginal doses of 0·8 mg, up to three or four doses given at 24-h intervals to induce abortion in 720 women with pregnancies of up to 9 weeks, failed to terminate 7% of

pregnancies, and induced complete abortion in 89% of the women. In another study of 125 women with pregnancies of up to 8 weeks, the corresponding figures were 5% and 88%, respectively.[10] Thus, when misoprostol is given vaginally, administration intervals do not seem to have a major role in efficacy of the treatment.

Our study clearly shows, however, the effect of interval on efficacy for sublingual administration—the 3-h interval between doses was significantly more effective than was the 12-h interval. This finding could be explained by the fact that after sublingual administration of misoprostol, uterine contractility seems to start decreasing in about 2–3 h.[6] Therefore, for women who prefer sublingual administration, the short interval should be used otherwise the continuing pregnancy rate increases.

According to our protocol, vacuum aspiration was done if abortion was not complete at the 2-week follow-up. Thus, only abortions that were complete at this time point were regarded as successful terminations. Many of the 107/2046 (5%) incomplete abortions and 83/2046 (4%) missed abortions might have become complete with longer follow-up. However, an increased waiting time would not have reduced the rate of continuing pregnancies.

Pharmacokinetic studies show that serum concentrations of misoprostol stay high for at least 4 h after vaginal administration of the drug, and uterine contractility continues to increase beyond this period.[3] We do not know how long it takes until the serum concentration starts falling and uterine contractility starts weakening after a single vaginal administration of misoprostol. Furthermore, no studies have investigated the pharmacokinetics of misoprostol during repeat administration. Clinically we can suspect that accumulation of the drug probably takes place during 3-h vaginal administration, and perhaps also when given sublingually.

We also noted that with increasing gestational length the efficacy of misoprostol regimens decreases, since the risk of failure was twice as high for women with 8–9 weeks of gestational age compared with those with 7 weeks or less. This finding is similar to previous studies using misoprostol only regimens[7] and the combined regimen of misoprostol after mifepristone pretreatment, especially when misoprostol is given orally.[13] Whether administration of additional doses of misoprostol to women with 8–9 weeks of gestational age improves the efficacy is unknown. However, since half the women in the 12-h groups already aborted after the first dose, less than three doses might be sufficient in very early gestations.

The efficacy of the regimen is very important, because failures—ie, continuing pregnancies—are sometimes difficult to recognise. Although misoprostol has proved to be safe and well tolerated, congenital malformations have been reported in association with failures after attempts to induce abortion with the drug.[17] Malformations might be caused by disturbed blood supply to the developing embryo during contractions, since mutagenicity studies have been negative and misoprostol proved not to be embryotoxic, fetotoxic, teratogenic, or carcinogenic.[18] Whatever the cause of malformations, if there is a possibility that the treatment failures are associated with an increased risk of malformations, regimens with high efficacy should be used.

Pain was the most common symptom reported after the first dose of misoprostol, and its intensity increased after the second and third dose when the drug was given at 3-h intervals. When 0·8 mg of misoprostol was given vaginally 36–48 h after mifepristone pretreatment, around 60–75% of women reported pain.[1] Since only one dose of misoprostol is usually needed after mifepristone pretreatment to induce abortion in pregnancies of up to 9 weeks' gestation, the duration of pain is shorter than when multiple doses are needed. Therefore, when misoprostol is used alone, adequate pain medication should be provided during the whole abortion process.

The most common drug-related side-effects were diarrhoea and chills or shivering, the incidence of which were slightly higher in sublingual groups than in vaginal groups. Fever was significantly more common in women who received misoprostol at 3-h intervals than at 12-h intervals. These side-effects seem to be related to misoprostol dose and serum concentrations.

We believe that this trial has internal validity because women were randomly assigned to treatment groups, random allocation was concealed, and sample size was calculated according to the pre-stated hypothesis. This trial also has external validity since women from several different populations were enrolled. However, because of our rather strict eligibility criteria, results might not apply to wider populations. Unwillingness to return for follow-up visits was the most common reason for exclusion from the study, but a follow-up visit is also important in routine services to confirm that pregnancy was terminated. We were perhaps too cautious to exclude women with uterine scar from this study, since uterine scar is unlikely to increase rupture risk in early first trimester.

Contributors

HvH, in collaboration with the members of the steering committee, was responsible for the conception of the trial and selection of centres. HvH and GP prepared the protocol. KA, EC, MG, RE, AK, SM, RS, RN, TMH, NDV, NTNP, and HTDT contributed to the final trial protocol and implemented the trial in their respective countries. HvH and GP supervised the trial. GP and NTMH were responsible for the statistical analysis and AP for the data management. HvH, GP, and NTMH wrote the paper with inputs from the investigators.

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Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The study was funded by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. We thank the members of the data and safety monitoring board for their contribution to interim analyses and their valuable comments on the report, and Paul Van Look for his critical review of the report in its final stages.

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