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Mifepristone in Combination with Misoprostol for the Termination of Pregnancy at 8−16 Weeks' Gestational Age: A Multicentre Randomized Controlled Trial

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Objective *To compare the efficacy and safety of medical abortion of different regimens for termination of pregnancy at 8−16 weeks of gestation.*

Methods *Healthy pregnant women requesting medical abortion at 8−16 weeks' gestation within 12 hospitals in Shanghai were randomly allocated to four treatment*

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groups. Three intervention groups were given mifepristone 200 mg as a single dose then 24 h later misoprostol 600 μg at 3 h intervals vaginally, orally or vaginally followed by orally, respectively. Control group was given mifepristone 100 mg for 2 d, followed at 48 h by initiation of misoprostol 600 μg vaginally every 12 h. The primary outcome measures were the successful abortion rate, the induction-to-abortion interval, vaginal bleeding and side effects.

Results *Efficacy outcomes were analyzed for 1 112 women (92.67%), excluding 88 protocol violations. Termination successful rates were similar among the four groups from 97.1% to 97.8%. The average dose of misoprostol and the incidence of side effects in control group were lower than those in three intervention groups. Stratified analysis showed that the interval of induction-to-abortion at gestation of 11−16 weeks was decreased in control group.*

Conclusion *The four regimens have the similar termination successful rates in spite of different administration intervals or routes. Control group was recommended for the advantages of reduced dose of misoprostol and fewer side effects.*

Key words: medical abortion; 8−16 weeks' gestation; randomized controlled trial (RCT)

Medical abortion is a good alternative to surgical abortion and used in 19 countries including China[1,2]. Most abortions are carried out in the first trimester and only 5%−10% in the second trimester[3]. Medical regimens of mifepristone in combination with misoprostol for women undergoing abortion at 8−16 weeks' gestation are used off-label in China and the majority of abortions at these gestations are undertaken surgically[4-6]. While the medical method has become standard of care for second trimester abortions in many countries and is recommended in evidence-based guidelines like in the Royal College of Obstetrician and Gynaecologist (RCOG) of UK or the society of family planning[2,7]. Many studies demonstrate that medical abortion at mid-trimester is a safe, acceptable and effective alternative to surgical abortion[8-13].

The existing medical methods use a variety of regimens, including different doses, administrative routes and intervals of medication, so it is difficult for the clinician to choose the optimal strategy[2,12-14]. To our knowledge, there are few large studies comparing the efficacy of mifepristone in combination with prostaglandins to induce abortion in late first trimester and early second trimester. The most popular regimen of medical abortion at 8−16 weeks' gestation in Shanghai is mifepristone 100 mg taken for 2 d, followed by initiation of misoprostol 600 μg vaginally every 12 h, which has been confirmed efficacy for medical termination[4-6]. The main disadvantage of this regimen is the longer hospital stay (more than 3 d), which is an influence on the optimal use of hospital resources. One review about

mid-trimester termination of pregnancy (TOP) shows that the optimal route for misoprostol administration is vaginally, preferably using tablets at 3 h intervals[13]. The pharmacokinetic studies show the plasma level of misoprostol acid can only maintain approximate 6 h after vaginal administration, which gives a challenge to the current regimen in Shanghai[15]. Therefore it would be useful to develop new modified regimens of single dose mifepristone followed by initiation of misoprostol within 24 h, given, for example, every 3 h in order to substitute for, or complement, the standard regimen.

The hypothesis of this randomized controlled trial (RCT) is that regimens of single dose mifepristone 200 mg, followed in 24 h by initiation of misoprostol 600 μg at 3 h intervals is equivalent to the existing regimen in Shanghai. We classified misoprostol administration into three subgroups according to different routes (orally, vaginally or vaginally in combination with orally). Thus, we undertook a multicentre RCT to compare the efficacy, safety and acceptability of mifepristone followed by initiation of misoprostol at 3 h intervals within 24 h, given orally or/and vaginally, for TOP at 8–16 weeks' gestation compared with the control regimen.

Materials & Methods

Participants

The RCT was conducted at 12 hospitals in Shanghai between July 2009 and June 2011. Pregnant women at 8–16 weeks' gestation requesting medical termination were eligible for recruitment if they met the following criteria: 18–40 years old, singleton viable intrauterine pregnancy, ultrasonically estimated gestational age of 8–16 weeks (the amenorrhea duration from last menstrual period was 50–112 d) and normal clinical examination results. Exclusion criteria were suspected ectopic pregnancy, abnormal placenta location, hypertension or other organic diseases, genital tract infection, genital tract tumors, known allergy to mifepristone and misoprostol. Women wishing to participate had to give written consent.

Intervention

Women were randomly allocated into four groups. Women in group A and group B received mifepristone (New Hualian Pharma Co., China) 200 mg orally on the first day and misoprostol (New Hualian Pharma Co., China) 600 μg vaginally 24 h later. If products of conception were not expelled, a further 600 μg misoprostol was given vaginally (group A) or orally (group B) at 3 h intervals, with a maximum of four doses in total. In group C, mifepristone 200 mg was administered orally on the first day, misoprostol 600 μg was administered orally 24 h later. A further 600 μg misoprostol was given orally at 3 h intervals if products of conception were not expelled, up to a maximum of four doses in total. In group D, mifepristone 100 mg orally on the first day and second day, misoprostol 600 μg was administered vaginally on the third day (ie within 48 h). A further 600 μg misoprostol was given vaginally

at 12 h intervals if products of conception were not expelled, up to a maximum of three doses. In this study, group D was used as the control.

Randomization

The randomization was performed by opening consecutive sealed opaque envelopes containing a random number generated by computer. Random numbers were prepared by the trial statistician using a randomized block design with blocks of eight. Allocation of treatment was concealed by the sealed, sequentially numbered treatment packs, which were filled and labeled in accordance with the randomization list. The study did not use placebo control tablets, and it was difficult to blind for participants and providers because of the different time intervals and routes of administration.

Sample size

Sample sizes were calculated dependent on estimated differences in the termination successful rate at 24 h after the last misoprostol treatment. The regimen of mifepristone 200 mg and misoprostol vaginally would achieve a successful rate of 90% in previous study[17]. A sample size of 279 in each group has a power of 0.8 at 5% significance in two-side test to detect a difference of 10% in successful rate. Given the dropout was about 10%, 300 women in each group were planned to recruit and therefore the total were 1 200.

Outcome

The primary outcome measure was the termination successful rate at 24 h after the last misoprostol treatment. Success was defined as the expulsion of fetus, irrespective of whether surgical evacuation was necessary because of incomplete abortion or heavy bleeding. Complete abortion was defined as the expulsion of all products of conception. Incomplete abortion was defined as incomplete removal of conception products and confirmed by histological examination. Secondary outcome measures included induction-to-abortion interval, side effects, the amount of vaginal bleeding and the number of repeated misoprostol administrations.

Procedures

Women undergoing medical termination were asked to attend gynecology ward and assigned by doctors. Following administration of misoprostol, the pulse, blood pressure and temperature were monitored every 3 h. After delivery of the fetus and placenta, 20 IU oxytocin was given intramuscularly. If abortion failed, further intervention could be medical or surgical and depended on the attending doctor's experience and skill. Surgical evacuation was offered if there was clinical evidence of retained placenta tissue, heavy bleeding or suspicion of incomplete abortion. The follow-up was carried out at 2 weeks and 8 weeks after treatment, or earlier if medically indicated. At the follow-up clinic, the patient was asked about the restoration of menstruation, any complications and preferred routes of

misoprostol administration.

Statistical analysis

Data were collected and recorded by trained staff and reviewed by the principal investigators at each hospital and later entered into Epi database and double checked. Data were expressed as mean ± SD ($\bar{x} \pm s$) or mean ±SE ($\bar{x} \pm s_x$) or percentage (%). Analysis was performed using SPSS 16.0. Distribution of samples was assessed using the Kolmogorov-Smirnov *Z* test. Differences in continuous variables were analyzed with ANOVA test for normally distributed data and the Mann-Whitney *U* test for skewed data. Comparisons for categorical variables were tested with χ^2 test and Fisher exact test where were appropriate. A stratified efficacy analysis was done by gestational age.

Ethical aspects

The study was registered with Chinese Clinical Trial Centre (No.: ChiCTR-RC-11001438) and was approved by the Ethics Committee of Shanghai Institute of Planned Parenthood Research. All participants had informed the trial and written the consent.

Results

A total of 1 200 women who requested TOP agreed to participate in the study. Of these, 88 women with protocol violations were excluded after randomization, including 87 women who did not receive doses at required intervals and one woman who was discovered hypertension after mifepristone administration and dropped out research. The intention-to-analysis was not used in this study. Figure 1 shows the trial profile.

Table 1 Baseline characteristics

Item	Group A	Group B	Group C	Group D
n	271	277	285	279
Age (year)	27.3 ± 6.3	27.0 ± 6.1	27.2 ± 5.6	28.0 ± 5.7
Weight (kg)	55.8 ± 8.4	53.5 ± 7.3	53.95 ± 7.2	54.1 ± 7.8
Height (cm)	160.5 ± 9.9	162.4 ± 8.2	161.4 ± 4.4	161.0 ± 6.2
Haemoglobin (g/L)	120.96 ± 10.20	122.52 ± 10.17	119.10 ± 10.50	118.28 ± 13.78
History of pregnancy (%)	66.8 (181/271)	62.5 (173/277)	63.5 (181/285)	68.5 (191/279)
History of live birth (%)	60.3 (94/271)	60.4 (99/277)	55.5 (90/285)	61.2 (101/279)
Menstrual cycles (d)	30.8 ± 5.1	30.7 ± 5.1	30.7 ± 5.8	30.2 ± 5.17
Menstrual duration (d)	5.6 ± 1.9	5.4 ± 1.2	5.3 ± 1.1	5.9 ± 1.9
Gestational age (week)				
8–10 (%)	41.0 (111/271)	44.4 (123/277)	41.1 (117/285)	33.0 (92/279)
11–12 (%)	22.9 (62/271)	26.7 (74/277)	25.5 (73/285)	24.7 (69/279)
13–14 (%)	24.0 (65/271)	19.5 (54/277)	20.4 (58/285)	24.0 (67/279)
15–16 (%)	12.1 (33/271)	9.4 (26/277)	13.0 (37/285)	18.3 (51/279)
Mean ± SD	10.2 ± 2.1	9.9 ± 2.0	10.1 ± 2.1	10.6 ± 2.2

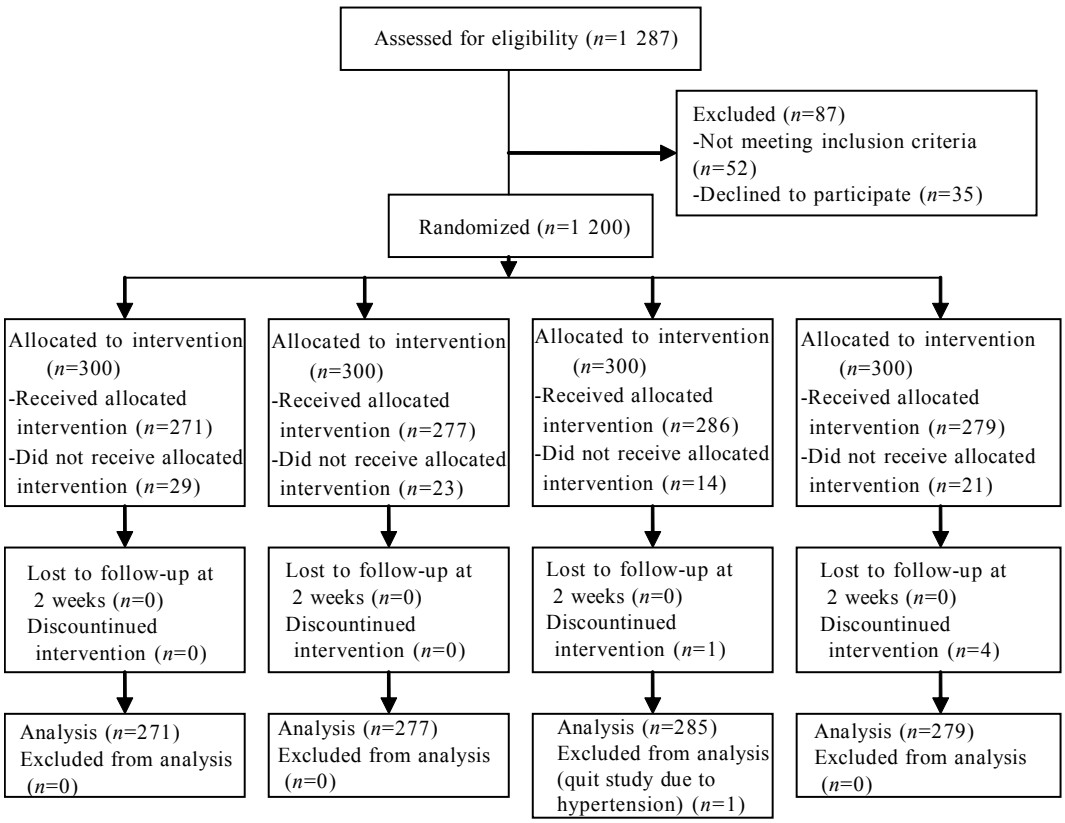

Figure 1 Trial profile

Table 1 shows baseline characteristics of the sample. The mean age, pregnancy history, menstrual cycle and duration were not different among four groups. The termination successful rates were high in all groups (97.1% to 97.8%) with no significant differences ($P>0.05$) (Table 2). The complete abortion rates at 2-week follow-up proved to be equivalent among the 4 groups ($P>0.05$). In group D, the dose of misoprostol was significantly lower at 0.72 mg and induction-to-abortion intervals (5.8 h) was significantly decreased compared with other 3 groups ($P<0.05$). No woman needed blood transfusion. Although the vaginal blood loss in group B was significantly lower than that in group C, post hoc multiple comparisons showed no difference among the other groups ($P>0.05$). The duration of bleeding and the median interval between treatment and first mense were similar in all groups ($P>0.05$).

A stratified analysis of efficacy by gestational age was performed for the complete abortion rate and induction-to-abortion interval. The results showed that the complete abortion rate at 8−10 weeks was 78.2% in group D, significantly lower than that in other groups at the same gestational age ($P<0.05$), while no differences were found for the complete abortion rate among 4 groups at the higher gestational age (11−16 weeks) ($P>0.05$) (Figure 2A). The induction-to-abortion interval was similar among the 4 groups at 8−10

Table 2 Abortion outcomes in the four treatment groups

Item	Group A	Group B	Group C	Group D	*P*
n	271	277	285	279	
Successful rate (%)	97.4 (264/271)	97.8 (271/277)	97.2 (277/285)	97.1 (271/279)	>0.05
Complete abortion (%)	93.7 (254/271)	88.4 (245/277)	89.1 (254/285)	88.5 (247/279)	
Incomplete abortion (%)	3.7 (10/271)	9.4 (26/277)	8.1 (23/285)	8.6 (24/279)	
Continuing pregnancy (%)	2.6 (7/271)	2.2 (6/277)	2.8 (8/285)	2.9 (8/279)	
Dose of misoprostol					–
Vaginal (μg)	678 ± 300	372 ± 201	–	432 ± 180	
Oral (μg)	–	414 ± 282	786 ± 330	–	
Oxytocin requirement (%)	54.0 (142/263)	49.4 (132/267)	43.5 (120/276)	61.0 (166/272)	0.00
n=1 078 (34)					
Induction-to-abortion interval (h)					>0.05
Median	5.0	5.1	4.8	4.5	(D *vs*
Mean ± SD	6.5 ± 5.0	6.2 ± 4.8	6.0 ± 6.3	5.8 ± 4.7	others)
Range	0.9–34.0	0.2–40.5	0.5–59.0	0.6–39.2	
Vaginal bleeding in abortion (<2 h)(ml)					0.014
Median	40.0	40.0	40.0	50.0	(B *vs* C)
Mean ± SD	54.1 ± 44.5	46.7 ± 37.6	58.1 ± 46.4	52.6 ± 44.1	
Range	5–350	5–350	5–350	5–350	
Vaginal bleeding in 2–24 h (ml)					>0.05
Median	50.0	50.0	50.0	50.0	
Mean ± SD	46.7 ± 30.4	47.0 ± 38.6	47.5 ± 29.3	47.9 ± 27.1	
Range	5–180	5–450	5–150	10–200	
Haemoglobin (g/L)					0.038
Median	116.0	118.0	114.0	115.0	(D *vs* B)
Mean ± SD	114.5 ± 11.6	116.5 ± 10.8	113.4 ± 10.4	113.3 ± 10.0	
Range	70–137	76–141	85–141	73–136	
Surgical evacuation	25.5 (69/271)	29.6 (81/274)	30.5 (85/279)	54.9 (152/277)	0.00
Duration of bleeding (d)					>0.05
Cases (except surgical)	188	177	159	120	
Median	10.0	10.0	10.0	9.0	
Mean ± SD	10.8 ± 5.4	11.3 ± 7.5	10.3 ± 5.3	10.1 ± 5.5	
Range	2–40	2–67	3–42	3–30	
Interval between treatment and first mense (d)					>0.05
Median (range)	35.0	36.0	36.0	36.0	
Mean ± SD	36.1 ± 7.2	35.9 ± 7.0	37.8 ± 7.9	38.5 ± 10.4	
Range	19–69	15–62	23–75	23–97	

n= the actual number (missing number)

weeks, but at 11–16 weeks it was significantly decreased in group D compared with other 3 groups ($P<0.05$) (Figure 2B).

The results suggested that the complete abortion rate at 8–10 weeks in group D was lower than that in other groups ($P<0.05$), while no significant differences were found with an

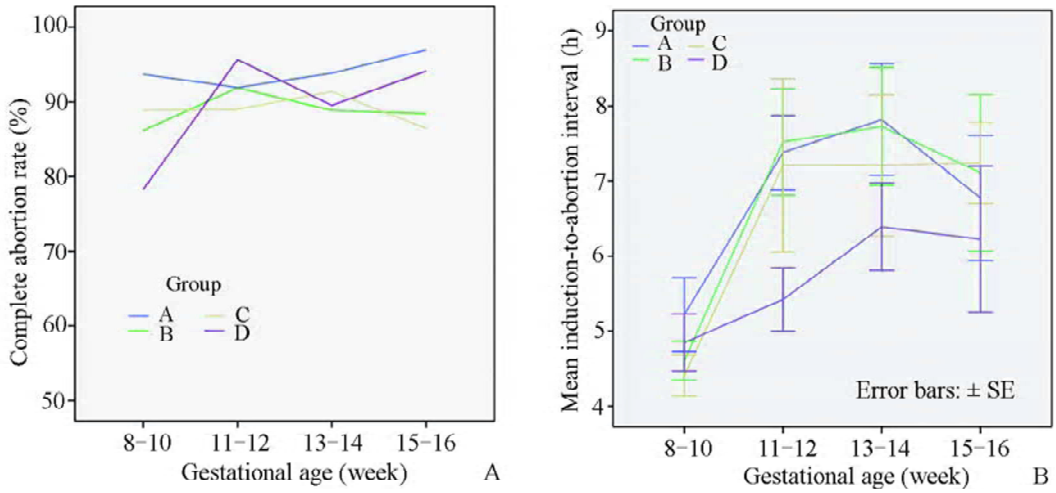

Figure 2 Efficacy of four regimens was influenced by gestational age

increase in gestational age (Figure 2A). The interval of induction-to-abortion at 8−10 weeks was similar in the 4 groups, but the intervals in group D was significantly decreased compared with other 3 groups at 11−16 weeks (P<0.05) (Figure 2B).

Surgical intervention was conducted in 387 women and the abortion outcome was present in Table 3. The surgical intervention was performed in 335 women (86.6 %) during hospitalization and 52 (13.4%) during the follow-up. The reasons for surgical intervention were incomplete placenta removal (31.27%), heavy bleeding (14.73%), placenta retained (8.50%) and missing data (45.48%). The number of women with curettage in group D was much higher at 54.9% compared with other groups. More than half of them were pathological confirmed as deciduas and inflammatory tissues, which provided insufficient indicators for curettage. For the women with curettage, the induction-to-abortion interval was about 4 h, the duration of bleeding was in the range of 3.8−4.5 d, the blood loss in 2 h and between 2− 24 h in women with curettage appeared significantly more than women without curettage (P<0.05). The pathological diagnosis was mainly deciduas (55.2%), placenta and villus (35.3%), inflammatory tissues (8.9%) and others (0.6%).

The incidence rate of side effects after receiving misoprostol was significantly lower in group D (75.3%) compared with other groups (P<0.05) (Table 4). Nausea and vomiting were recorded significantly less frequently in group D compared with group A and group B (P<0.05). The incidence of nausea and pruritus in group C was significantly higher than that in other 3 groups (P<0.05). Other side effects did not differ significantly among the four groups and none were reported during the follow-up.

Acceptability of medical termination regimens was investigated at 8-week follow-up and showed a significant difference among the four groups (Table 5). The highest rate of satisfactory was reported in group D (92.25%), while the lowest satisfaction rate was in group

Table 3 Abortion outcome and pathological diagnosis of women with surgical intervention

Item	Group A	Group B	Group C	Group D	*P*
n	69	81	85	152	
Gestational age (week)					<0.05
8–10 (%)	13.8 (15/109)	28.7 (37/129)	24.8 (32/129)	39.0 (39/100)	
11–12 (%)	31.7 (20/63)	22.1 (15/68)	26.2 (16/61)	61.0 (36/59)	
13–14 (%)	33.9 (19/56)	35.0 (14/40)	42.0 (21/50)	65.4 (34/52)	
15–16 (%)	35.9 (14/39)	44.1 (15/34)	34.9 (15/43)	63.1 (41/65)	
Abortion outcome (%)					>0.05
Complete abortion	78.26 (54/69)	65.43 (53/81)	67.06 (57/85)	80.92 (123/152)	
Incomplete abortion	13.04 (9/69)	29.63 (24/81)	27.06 (23/85)	15.13 (23/152)	
Continuing pregnancy	8.70 (6/69)	4.94 (4/81)	5.88 (5/85)	3.95 (6/152)	
Induction-to-abortion interval (h)					>0.05
Median	5.0	5.1	5.5	4.7	
Mean ± SD	6.4 ± 4.4	6.5 ± 5.8	6.9 ± 6.7	6.0 ± 4.2	
Range	0.9–27.4	2.0–32.3	1.2–52.5	1.3–29.5	
Vaginal bleeding in abortion (<2 h)(ml)					<0.05
Median	40.0	30.0	50.0	50.0	(C vs
Mean ± SD	63.7 ± 61.9	51.5 ± 59.6	65.0 ± 63.0	58.9 ± 50.3	B)
Range	5–350	5–350	10–350	10–350	
Vaginal bleeding in abortion (2–24 h)(ml)					>0.05
Median	50.0	50.0	50.0	50.0	
Mean ± SD	57.1 ± 36.9	54.7 ± 54.0	51.9 ± 31.6	51.0 ± 25.2	
Range	10–180	5–450	5–150	10–200	
Haemoglobin (g/L)					>0.05
Median	109.0	114.5	113.0	112.0	
Mean ± SD	109.7 ± 15.1	115.1 ± 11.2	112.4 ± 11.1	112.3 ± 8.2	
Range	70–137	76–141	88–133	87–131	
Pathological diagnosis *n*=348 (39)					>0.05
Placenta and villus	27	23	27	46	
Deciduas	37	43	51	61	
Inflammatory tissue	4	10	5	12	
Other	0	1	1	0	
Total	68	77	84	119	

n= the actual number (missing number)

C (70.61%). In addition, the proportion of women inclined to prefer oral route of misoprostol were dramatically higher than that of choosing vaginal route ($P<0.05$).

Discussion

In our study, the results of the multicentre RCT indicated that three modified regimens of mifepristone 200 mg followed within 24 h by initiation of 600 μg misoprostol orally or

Table 4 Side effects experienced by women receiving misoprostol in this trial

Item	Group A	Group B	Group C	Group D
n	271	277	285	279
Incidence rate (%)	81.2 (220/271)*	86.6 (240/277)*	86.3 (246/285)*	75.3 (210/279)
Nausea (%)	35.9 (97/271)[b]	35.6 (100/277)[b]	47.5 (134/285)[b]	25.0 (69/279)[a]
Vomiting (%)	12.6 (34/271)[b]	14.6 (40/277)[b]	8.2 (23/285)[a]	8.3 (23/279)[a]
Headache (%)	2.6 (7/271)	1.5 (4/277)	1.8 (5/285)	1.1 (3/279)
Dizziness (%)	5.9 (16/271)	4.0 (11/277)	5.3 (15/285)	2.9 (8/279)
Diarrhoea (%)	1.9 (5/271)	1.1 (3/277)	1.4 (4/285)	1.5 (4/279)
Fever (%)	14.8 (40/271)	9.9 (27/277)	8.5 (24/285)	10.1 (28/279)
Shivering (%)	3.7 (10/271)	4.0 (11/277)	3.9 (11/285)	2.9 (8/279)
Chilling (%)	4.8 (13/271)	5.1 (14/277)	5.7 (16/285)	4.7 (13/279)
Pruritus (%)	3.0 (8/271)[b]	2.2 (6/277)[b]	7.1 (20/285)[a]	1.8 (5/279)[b]
Waist soreness (%)	24.4 (66/271)	20.2 (55/277)	24.1 (68/285)	30.1 (83/279)
Tender breast (%)	1.5 (4/271)	1.8 (5/277)	2.8 (8/285)	1.1 (2/279)
Abdominal pain (%)	50.0 (135/271)	52.4 (143/277)	50.4 (142/285)	60.6 (112/279)
Tiredness (%)	10.3 (28/271)	15.4 (42/277)	12.8 (36/285)	8.3 (23/279)

*: $P<0.05$, compared with group D

a, b: $P<0.05$, the comparison between the groups of different letters was significantly different

Table 5 Acceptability of medical termination and preferred route of misoprostol administration by participants at 8-week follow-up

Item	Group A	Group B	Group C	Group D	*P*
Acceptability of medical termination *n*=1 022 (90)					0.00
Satisfactory (%)	80.08 (193/241)	85.66 (209/244)	70.61 (197/279)	92.25 (238/258)	
Moderate (%)	16.60 (40/241)	12.70 (31/244)	19.35 (54/279)	6.59 (17/258)	
Dissatisfactory (%)	2.07 (5/241)	0.41 (1/244)	4.66 (13/279)	0.39 (1/258)	
Refuse to answer (%)	1.24 (3/241)	1.23 (3/244)	5.38 (15/279)	0.78 (2/258)	
Preferred route of misoprostol *n*=1 018 (94)					0.00
Orally (%)	67.08 (161/240)	52.48 (127/242)	87.41 (243/278)	60.47 (156/258)	
Vaginally (%)	32.92 (79/240)	47.52 (115/242)	12.59 (35/278)	39.53 (102/258)	

n= the actural number (missing number)

vaginally at 3 h intervals had equivalent effectiveness to the control regimen for women who want to avoid surgery at gestations 8−16 weeks.

To date, medical abortion is not licensed for use in women at 8−16 weeks' gestation in China so there is no uniform regimen with strong evidence to inform clinical doctors. There are multiple abortion induction regimens available, including differing schedules of mifepristone, different routes and dose schedules of misoprostol administration[2,12], but this is the first study to compare the efficacy, safety and acceptability of the four regimens in a large RCT to our knowledge. In our study, similar successful rates in the four groups indicated acceptable abortion outcomes in spite of differences in administration interval and route. Control group

did demonstrate superiority in shorter induction-to-abortion intervals, lower misoprostol requirement and fewer side effects, so it was recommended as an optimal choice.

Relative effectiveness and acceptability of two routes of administration (oral or/and vaginal) have been evaluated. A vaginal "loading" dose of 600 μg of misoprostol followed by 600 μg vaginally or orally every 3 h may be more effective[13,16]. It was believed that the use of misoprostol vaginally as the first dose could lead to more effective cervical priming, but there was no advantage in the vaginal administration of subsequent doses[18]. Oral and vaginal routes of administration have similar abortion outcomes in most circumstances; oral ingestion may be equally effective to other routes when used for repeat doses or as the primary route after mifepristone pretreatment[13]. However, oral administration is convenient and preferable to women both in our study and in previous reports[16].

The management of women who fail to abort has not been previously studied systematically. Our data showed that the proportion of women who experienced curettage was 34.8%, including the total of 123 women with the pathological reports of placenta villus. We did not find differences in the successful rate and induction-to-abortion interval for the 4 groups of women with curettage, but they had more excessive vaginal bleeding and relative shorter duration of bleeding compared to those without curettage. The percentage of curettage was higher in the subgroup of gestage of 15−16 weeks than 8−10 weeks. To our surprise, the pathological results showed that nearly half women having curettage proved to be deciduas and inflammatory tissue. This was linked with unnecessary curettage abortion processes, partly due to loose definitions of surgical indications. So we should strongly recommend stricter surgical indications after medical abortion. In group D, the higher percentage of curettage was present, it may be a weakness in the multiple RCT, for curettage was used as a routine in some hospitals and did not strictly obey our protocol. The induction-to-abortion interval was influenced by gestational age. For the subgroups of 11−16 weeks, a shorter induction time was found in control group. The addition of mifepristone to misoprostol was found to improve cervical dilation yet increase procedure time and frequency of pre-procedural expulsions. Two-day cervical preparation using mifepristone was found to produce greater cervical preparation than 1 d[19]. Mifepristone can shorten the induction-to-abortion interval and reduce the required dose of misoprostol if it is given between 36−48 h before misoprostol administration[20]. The shorter induced times was reported in groups of women using a 2 d interval between mifepristone and vaginal misoprostol than those using 1 d interval (7.5 h *vs* 9.8 h)[21]. So the advantage of shorter induction time in control group may be due to the mifepristone pretreatment for 2 d.

Abdominal pain was the most common symptom reported after the first dose of misoprostol, and its intensity increased when the repeated dose was given at 3 h intervals. The incidence of all side effects was slightly higher in the 3 groups of 3 h interval than the control. These side-effects seemed to be related to serum higher misoprostol concentration

in the groups of 3 h intervals. In conclusion, this study has identified the efficacy, safety and acceptability of four regimens for TOP at 8−16 weeks' gestation. The findings show that the four regimens have similar abortion rates in spite of differing intervals and routes. The advantages of control group were the reduced dose of misoprostol required, fewer side effects and shorter induction-to-abortion interval in the subgroup of 11−16 weeks. So the regimen of mifepristone 200 mg following in 48 h by initiation of misoprostol 600 μg vaginally at 12 h intervals is recommended as the optimal choice.

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