

Comparing the World Health Organization-versus China-recommended protocol for first-trimester medical abortion: a retrospective analysis

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Objective: To compare the effectiveness, in terms of complete abortion, of the World Health Organization (WHO)- and the China-recommended protocol for first-trimester medical abortion.

Methods: A retrospective analysis of clinical data from women presenting for first trimester medical abortion between January 2009 and August 2010 at reproductive health clinics in Qingdao, Xi'an, Nanjing, Nanning, and Zhengzhou was conducted. One clinic in Qingdao administered the WHO-recommended protocol (200 mg mifepristone orally followed by 0.8 mg misoprostol buccally 36–48 hours later). Four clinics in the other locations provided the China-recommended procedure (Day 1: 50 mg of mifepristone in the morning, 25 mg in the afternoon; Day 2: 50 mg of mifepristone in the morning, 25 mg in the afternoon; Day 3: 0.6 mg oral misoprostol). Data on reproductive and demographic characteristics were extracted from clinic records, and complete termination was determined on day 14 (post-mifepristone administration).

Results: A total of 337 women underwent early medical abortion (167 WHO- and 170 China-recommended procedures). Complete abortion was significantly higher among women who had the WHO protocol than those who received the China protocol (91.0% vs 77.7%, respectively; $P < 0.001$). Women using the China-recommended protocol were three times more likely to require an additional dose of misoprostol than women using the WHO protocol (21.8% vs 7.8%, respectively; $P < 0.001$), and had significantly more bleeding on the day of misoprostol administration (12.5 mL vs 18.5 mL; $P < 0.001$).

Conclusion: This clinical audit provides preliminary evidence suggesting the WHO-recommended protocol may be more effective than the China-recommended protocol for early medical abortion. A larger scale study is necessary to compare the methods' effectiveness and acceptability.

Keywords: medical abortion, misoprostol, mifepristone, China, first-trimester termination

Introduction

Since the synthesis of prostaglandins in 1969¹ and antiprogesterone in the 1980s,² mifepristone–misoprostol medical abortion has provided an important alternative to surgical methods for elective termination of pregnancy. Many studies have been conducted to identify better ways to deliver medical abortion methods, including the use of single drugs, varying the timing and routes of administration, and the use of different dose regimens.^{3–7} The World Health Organization (WHO) recommends the

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combination of 200 mg mifepristone followed by 0.8 mg misoprostol 36–48 hours later for first-trimester termination (gestations up to 63 days since last menstrual period).⁸ This regimen results in $\geq 96\%$ complete abortion, and $\leq 1\%$ continuing pregnancy.²

Different combinations of mifepristone and misoprostol are being used in various settings.⁹ In 2005, the majority (84.6%; 22 million) of the 26 million women who used a mifepristone-misoprostol regimen to terminate an unintended pregnancy lived in China.¹⁰ Since the approval of mifepristone as an abortifacient in 1988, the widely accepted medical abortion protocol in China comprised 150 mg mifepristone administered in four small doses across 2 days (Day 1: 50 mg of mifepristone in the morning (AM), 25 mg in the afternoon (PM); Day 2: 50 mg of mifepristone in the AM, 25 mg in the PM), followed by 0.6 mg oral misoprostol on the third day.¹¹ Approximately two million women in China use this regimen annually,¹ with high reported success rates (90%–97%) and client satisfaction ($\geq 80\%$).¹¹

Although the WHO- and China-recommended medical abortion protocols have been used by millions of women for early termination, there has been no direct comparison of the effectiveness of these two methods. It is unclear whether the lower dose of misoprostol affects the effectiveness of the Chinese method. It is also unknown whether there is any difference in the clinical process, in terms of duration of the procedure and the amount of bleeding.

A retrospective analysis of clinical data was conducted to compare the effectiveness of the WHO- and China-recommended medical abortion protocols for first-trimester termination of pregnancy at Marie Stopes International China (MSI China) clinics located in Qingdao, Xi'an, Nanjing, Nanning, and Zhengzhou.

Material and methods

Retrospective data from women presenting for first-trimester medical abortion at MSI China clinics in Qingdao, Xi'an, Nanjing, Nanning, and Zhengzhou, between January 2009 and August 2010, were analyzed. Gestational age was determined by last menstrual period and ultrasound. Women with a known allergy to either mifepristone or misoprostol, suspicion of ectopic pregnancy, chronic adrenal failure, concurrent long-term corticosteroid therapy, history of hemorrhagic disorders, concurrent anticoagulant therapy, or inherited porphyria were ineligible for medical terminations.

The MSI China clinic located in Qingdao administered the WHO-recommended medical abortion protocol, while

the four clinics in Xi'an, Nanjing, Nanning, and Zhengzhou provided the Chinese-recommended procedure. Because this was a pilot phase of introducing the WHO-recommended medical regimen, only clinical staff at Qingdao were trained to deliver the protocol.

These five clinics were chosen because they are operated by MSI China. Prior to the medical abortion procedure, women's characteristics including age, weight, number of births, number of pregnancies, and diameter of the sac tissue were recorded (per clinical standard practice). After informed consent was obtained, individuals who presented at the MSI China clinic in Qingdao underwent the WHO-recommended procedure, which consisted of 200 mg oral mifepristone followed by 0.8 mg of buccal misoprostol 36–48 hours later. If no bleeding occurred 3 hours after misoprostol administration, an additional dose of 200 μ g misoprostol was given buccally. If no bleeding was observed after a further 2 hours, one more dose of 200 μ g buccal misoprostol was administered. Women who accessed MSI China clinics in Xi'an, Nanjing, Nanning, and Zhengzhou underwent the China-recommended procedure: Day 1: 50 mg oral mifepristone in the AM, then 25 mg in the PM; Day 2: 50 mg oral mifepristone in the AM, then 25 mg in the PM; Day 3: Oral administration of 0.6 mg misoprostol. If no bleeding had occurred 3 hours after misoprostol administration, an additional dose of 200 μ g misoprostol was given orally. If no bleeding was observed after a further 2 hours, one more dose of 200 μ g misoprostol was orally administered. Under both protocols, patients attended the clinic for mifepristone and misoprostol administration, and they remained at the clinic for 4 hours after the administration of misoprostol for observation before being discharged.

All women received counseling on potential side effects and 500 mg paracetamol for pain management, and a follow-up appointment was scheduled for day 14 after the administration of mifepristone. Complete abortion was defined as passing of the products of conception without needing vacuum aspiration at the follow-up visit. At the 14-day follow-up visit, all women were assessed for the status of their abortion procedure by clinical examination and ultrasonography. Individuals with ongoing pregnancy, persistent nonviable pregnancy, or gestational sac were offered immediate surgical evacuation. Those with retained products at the 14-day follow-up visit confirmed by transvaginal ultrasound were given surgical evacuation. In addition to complete abortion, we analyzed the following information: (a) whether any additional doses of misoprostol were required;

(b) the time to expulsion of the gestational sac (in hours); and (c) the amount of bleeding on the day of misoprostol administration. Blood was collected in a container and measured in milliliters (mL) at the clinic after misoprostol administration.

All available data were retrieved from clinic records. Data management and analysis were carried out using Stata software (v. 11; Stata Corp, College Station, TX). Characteristics of the study participants and outcomes in each protocol group were compared using *t*-tests (for difference in means) and Z-tests (for difference in proportions). The primary outcome of this study was the proportion of successful abortions (defined as complete evacuation of the uterine contents without recourse to surgery by day 14). Secondary outcomes including the duration of the procedure and the amount of bleeding were also assessed. No ethics approval was obtained because this was a clinical audit.

Results

Study participants' characteristics

Of the 357 medical abortion cases that were seen in the five clinics between January 2009 and August 2010, 337 women with gestational ages up to 63 days were included in this analysis. A total of 167 women received the WHO-recommended procedure at the clinic in Qingdao, and 170 women underwent the Chinese-recommended protocol at clinics in Xi'an, Nanjing, Nanning, and Zhengzhou.

The characteristics of the women who received the WHO-recommended protocol were similar to the women who received the China-recommended protocol in terms of age, weight, and gestational age (Table 1). On average, women receiving the WHO protocol had more previous pregnancies than those that underwent the China protocol (2.2 vs 1.8 pregnancies; $P = 0.009$), and had a larger gestational sac (17.7 mm vs 15.9 mm; $P = 0.02$).

Medical abortion outcomes

Among all 337 cases, 84.3% achieved complete abortion. This success rate was significantly higher among women who received the WHO protocol compared to individuals who had the China procedure (91.0% vs 77.7%, respectively; $P < 0.001$) (Table 2).

Approximately 14.8% ($n = 50$ of 337) of women had no response 3 hours after taking the medical abortion drugs, and required an additional dose of misoprostol (200 µg). Women using the China protocol were three times more likely to require an additional dose of misoprostol than women using the WHO protocol (21.8% vs 7.8%, respectively; $P < 0.001$) (Table 2). Five women who underwent the China protocol (2.9%) still had no response 5 hours after the administration of misoprostol, and required a further additional dose of misoprostol (200 µg). No women in the WHO protocol group required a second additional dose.

There was no evidence of a difference in the time to expulsion of the gestational sac between women using the WHO protocol and those using the China-recommended protocol (3.1 hours vs 3.4 hours; $P = 0.10$) (Table 2). However, women in the WHO protocol group had significantly less bleeding on the day of the procedure than women in the China protocol group (12.5 mL vs 18.5 mL; $P < 0.001$).

Discussion

This analysis provides preliminary results that the WHO-recommended medical abortion protocol may be more effective than the China-recommended protocol for early medical abortion (gestations ≤ 63 days). There is evidence suggesting that women using the WHO-recommended protocol require fewer supplementary doses of misoprostol than those using the Chinese regimen, and experience less bleeding.

There are several key differences between the two protocols. First, a smaller dose of mifepristone is used in the China

Table 1 Characteristics of women, by medical abortion protocol

Characteristics Mean \pm standard deviation	Medical abortion protocol		P-value from t-test
	World Health Organization-recommended*	China-recommended**	
n	167	170	
Age (years)	24.2 \pm 4.5	23.3 \pm 4.7	0.09
Weight (kg)	50.9 \pm 7.1	49.8 \pm 5.6	0.13
Number of pregnancies	2.2 \pm 1.5	1.8 \pm 1.1	0.009
Number of births	0.2 \pm 0.5	0.1 \pm 0.3	0.005
Gestational age (days)	44.7 \pm 5.4	43.7 \pm 6.2	0.15
Diameter of gestational sac (mm)	17.7 \pm 7.1	15.9 \pm 7.6	0.02

Notes: *200 mg mifepristone followed by 800 µg misoprostol 36–48 hours later;^{14,15} **Day 1: 50 mg of mifepristone in the morning, 25 mg in the afternoon; Day 2: 50 mg of mifepristone in the morning, 25 mg in the afternoon; Day 3: 0.6 mg oral misoprostol.

Table 2 Proportion of complete abortion and details of medical abortion process, by protocol

	Medical abortion protocol		P-value for difference
	World Health Organization-recommended*	China-recommended**	
n	167	170	
Outcome			
Complete abortion % (n)	91.0 (152)	77.7 (132)	<0.001
Procedure details			
Required one additional dose of misoprostol % (n)	7.8 (13)	21.8 (37)	<0.001
Required two additional doses of misoprostol % (n)	0	2.9 (5)	0.03
Time to expulsion of gestational sac (hours)	3.1 ± 1.6	3.4 ± 1.4	0.10
Estimated amount of bleeding after misoprostol administration (mL)	12.5 ± 7.0	18.5 ± 13.6	<0.001

Notes: *200 mg mifepristone followed by 800 µg misoprostol 36–48 hours later;^{14,15} **Day 1: 50 mg of mifepristone in the morning, 25 mg in the afternoon; Day 2: 50 mg of mifepristone in the morning, 25 mg in the afternoon; Day 3: 0.6 mg oral misoprostol.¹¹

protocol than in the WHO protocol (150 mg vs 200 mg). However, a study conducted in nine countries among more than 2000 women showed similar efficacy in achieving complete abortion using 100 mg mifepristone compared to 200 mg mifepristone followed by misoprostol.¹² Second, the dosing schedule is more complex within the China-recommended protocol, with mifepristone taken in four small doses over 2 days, rather than in a single dose. Information on compliance with the protocol was not available in this audit, therefore the effect of the dosing intervals on compliance cannot be assessed. Third, a smaller dose of misoprostol is used in the standard China-recommended protocol compared to the WHO-recommended protocol (0.6 mg vs 0.8 mg, respectively). A trial of 2962 women comparing 0.4 mg with 0.8 mg misoprostol following 200 mg mifepristone showed higher risk of incomplete abortion and continuing pregnancy with the lower dose of misoprostol.¹³ Women who underwent the China-recommended protocol took additional doses of misoprostol to achieve successful termination. Finally, the interval between mifepristone and misoprostol administration is 24 hours in the China protocol, compared to 36–48 hours in the WHO protocol. A previous study showed that the 24- and 48-hour intervals have similar efficacy.¹² In addition, women who received the WHO-recommended regimen underwent buccal administration of misoprostol while individuals within the China-recommended group received oral administration of misoprostol. A recent Cochrane review showed that misoprostol administered orally is less effective than other routes of administration.¹⁴

There are limitations to this analysis. Due to the nature of a clinical audit with practical and resource constraints, there was no rigorous sampling strategy or random allocation of women

to groups. However, the basic demographic characteristics for women in both groups were similar, and contamination between the two medical abortion protocols was minimized because the clinic in Qingdao exclusively provided the WHO-recommended protocol while the other four clinics administered the China-recommended protocol. Providers at all health facilities underwent the same termination service training for each protocol. The small number of study participants in this study limits the generalizability of the results.

While we were able to collect women's demographic information and clinical indications, information on compliance and women's satisfaction were not available from the clinic record. Data on compliance to the protocol could reveal the effect of more complex dosing schedules on women's ability to adhere to the protocols and health care providers' confidence to deliver medical abortion regimens. Information on women's satisfaction would provide important measures of the acceptability of each regimen. Reducing the number of doses within the China-recommended protocol is one possible way to simplify the provision of medical abortion. Studies from various settings which reduced the number of clinic visits through home-based administration of misoprostol showed high acceptability (84%–96% acceptable).^{15–25} Finally, this clinical audit was not able to obtain information on side effects such as diarrhea and vomiting from the clinic records, which may be important factors for acceptability of regimens.

Our analysis provides preliminary evidence suggesting greater effectiveness of the WHO-recommended protocol for first-trimester medical abortion compared to the China-recommended regimen. However, this was not

a randomized controlled trial, and the results must be interpreted with caution. Given the wide usage of both protocols in China, a larger scale study to compare their effectiveness and acceptability would be appropriate in the future. Furthermore, analysis of the cost-effectiveness of each protocol may help to inform policy in China.

Disclosure

The authors declare no conflict of interest. Ngo TD, Park MH, and Yuanhoang X work for Marie Stopes International, an organization that provides comprehensive family planning and reproductive health services in China and worldwide. All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in this review; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in this review; (4) No nonfinancial interests that may be relevant to this analysis.

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