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Original Article

Mifepristone-misoprostol abortion in free-standing reproductive health clinics in India

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Abstract

Objectives: To explore the feasibility of providing a modified mifepristone-misoprostol regimen in four free standing reproductive health clinics in Delhi and Kolkata, India. *Methods:* A total of 676 women with pregnancy durations of 56 days or less received 200 mg mifepristone followed by in-clinic administration of 400 mcg misoprostol, orally in Delhi and sublingually in Kolkata. Confirmation of abortion status occurred in the clinic 12 days later almost exclusively on the basis of clinical examination. *Results:* Successful medical abortions occurred in 92.5% and 99.3% of the women with known outcomes in Delhi and Kolkata, respectively. Nearly all the women were "satisfied" or "very satisfied" with their treatment and indicated that they would choose medical abortion again if needed or would recommend it to others. *Conclusions:* Medical abortion can be safely, effectively and acceptably administered in day care reproductive health clinics in India. Carefully designed studies should compare the efficacy of sublingual and oral misoprostol following mifepristone.

Key words: medical abortion, mifepristone, misoprostol, India.

Introduction

Medical abortion using a combination of the antiprogestin mifepristone and a prostaglandin analogue was first approved in France in 1988. In the past 17 years, more than 30 countries, including some developing countries, have introduced a medical abortion regimen. In India, while abortion has been legal for over 30 years following the enactment of the Medical Termination of Pregnancy (MTP) Act, up to 90% of the estimated annual six million induced abortions are conducted illegally – in uncertified settings and/or by uncertified providers [1]. In April 2002, the Drugs Controller of India (DCI), approved 600 mg oral mifepristone followed by 400 mcg oral misoprostol to terminate pregnancies up to 49 days gestation.

Numerous studies, however, have confirmed that the efficacy of 200 mg mifepristone for early abortion [2-4] and both national medical professional organizations and the World Health Organization have endorsed reduced dose regimens [5-8]. Similarly, several studies have shown mifepristone-misoprostol to be effective beyond the 49 days gestational limit set by the DCI [9-10] and evidence based regimens up to 56 and 63 days gestation are used widely in North America and Europe [5-8]. Recently, researchers have begun investigating if alternative routes of misoprostol administration can improve efficacy. Pharmacokinetic

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analyses suggest that sublingual misoprostol acts as quickly as oral misoprostol, quicker than vaginal misoprostol and has a higher systemic bioavailability than all other routes of administration [11]. While only a few clinical studies have used a combination of mifepristone and sublingual misoprostol for early abortion, they have all had high efficacy [12-13].

India has one of the longest experience with medical abortion among developing countries, having participated in a series of international clinical studies since 1990 [10]. Findings from these studies uniformly demonstrated the safety, efficacy and acceptability of medical abortion in a variety of hospital and health care settings. The present study expands on these findings and examines the feasibility of providing a modified medical abortion regimen consisting of 200 mg mifepristone followed 48 hours later by either oral or sublingual misoprostol in gestations of 56 days or less in four free standing reproductive health clinics, run by a single nongovernmental reproductive health service provider, Parivar Seva Sanstha (PSS). PSS currently has 41 free standing reproductive health clinics spread across 21 states of India and performs an average of 87,000 abortions each year, accounting for roughly 15% of all the legal abortions reported to the Government of India.

Methods

We conducted a prospective study from June 2002 to December 2004 in four free standing reproductive health clinics of PSS, two each in Delhi and Kolkata. Each of the four clinics has legal, well established surgical abortion services and an annual abortion case load of approximately 2,500-3,500. None of the clinics have ultrasound facilities on site, but refer women for ultrasonography when necessary.

Women seeking abortions could participate if they had an intrauterine pregnancy of less than 56 days from the last menstrual period (LMP) on the basis of clinical examination, menstrual history, urine pregnancy test, had no contraindications to mifepristone or misoprostol, were 18 years or older, lived or worked within a distance of one hour travel from the clinic, and agreed to return for at least two follow up visits. Most of the women were informed about the study when they presented for surgical termination, although some learned about it through friends or other community members. As per the standard practice of PSS, the women paid approximately US$12 for their abortions. The Population Council's Institutional Review Board approved the study protocol and all the women gave written informed consent.

Upon enrollment at their initial clinic visit, the women received 200 mg oral mifepristone and were observed for 15 minutes. The women returned to the clinic 48 hours later for 400 mcg misoprostol, which was administered orally in Delhi and sublingually in Kolkata, and were observed for at least three hours. On the day they ingested misoprostol, the women were told to expect bleeding and/or pain and were given paracetamol for use at their discretion. Confirmation of the abortion status occurred in the clinic 12 days later, and was done almost exclusively on the basis of a clinical examination. Ongoing pregnancy was diagnosed by continuance of pregnancy symptoms with history of minimal or no vaginal bleeding, an increase in uterine size commensurate with fetal growth since last visit or presence of fetal heart activity on ultrasonographic examination. Complete abortion was diagnosed by the absence of above signs with the history of expulsion of the products of conception and a closed cervical os. Incomplete abortion was diagnosed by dilated cervical os. Those with a complete abortion were discharged from the study. Women with incomplete abortions were offered the choice of returning within one week for a final determination of the status of their pregnancy or immediate surgical intervention. Surgical intervention was performed if medically necessary, in cases of ongoing pregnancy or incomplete abortion, or if requested by the women at any time during the study. The women were advised to return to or call the clinic at any time if they had any problems or questions.

At each clinic visit, the providers collected clinical, experiential and acceptability data from the women using standardized questionnaires. The women also completed a daily symptom diary card during the weeks of the study. For calculating efficacy any woman who underwent a surgical completion for any reason was considered a failure. Following established methods, failures were classified as method or user choice [14].

Financial and practical limitations led us to select a sample size of 400 women each in Delhi and Kolkata. We postulated that at least 92% of the women using oral misoprostol and 97% of the women using sublingual misoprostol would have complete medical abortions. Therefore, a sample size of 400, using a 5% loss to follow up rate, provided a 95% confidence interval of 89.3%, 94.7% for oral misoprostol and

95.3%, 98.7% for sublingual misoprostol. Data were analyzed with STATA 7.0.

Results

Sample characteristics

Totally 676 women participated in the study, 400 in Delhi and 276 in Kolkata (Table 1). While the target sample size was 400 in each city, enrollment proved to be slow in Kolkata and thus the sample size was reduced so the study could be completed in a reasonable time frame. For 2% of the cases, gestational age of less than 8 weeks was confirmed on ultrasonography as clinical examination was inconclusive. At follow up, ultrasound was used to confirm the status of abortion in 3% of the women when the clinical examination was inconclusive. On an average, women at both the sites were in their mid twenties (Delhi: 27.2 years; Kolkata: 25.2 years), a large majority were married (Delhi: 92.5%, Kolkata: 88.0%) and about half (Delhi: 48.1%; Kolkata: 46.0%) reported one or more previous induced abortions. The mean gestational age of the women in Delhi and Kolkata was 6.1 weeks and 6.4 weeks, respectively.

Reasons for choosing medical abortion

Upon enrollment for the study, the women were asked to name up to two reasons for choosing medical abortion (Table 2). Most of the women in Delhi (73.7%) and Kolkata (57.6%) were motivated by a desire to

Table 1. Participant characteristics, by site.

	Delhi	Kolkata	p-value
Sample size, n (%)	400 (100.0)	276 (100.0)	
Age (years), mean ± SD	27.2±4.2	25.2±5.5	<0.0001
Completed schooling (years), mean ±SD	12.1±4.2	12.0±5.2	0.71
Married, n (%)	370 (92.5)	243 (88.0)	0.05
Primigravid, n (%)	55 (13.8)	100 (36.5)	<0.001
Prior elective abortion, n (%)	189 (48.1)	120 (46.0)	0.60
Gestational age (weeks), mean ± SD	6.1±0.7	6.4±0.8	<0.0001
Gestational age (weeks), n (%)			
≤5	28 (7.0)	16 (5.8)	
6	195 (48.7)	80 (29.0)	<0.001
7	129 (32.2)	110 (39.9)	
8	48 (12.0)	70 (25.4)	

Table 2. Reasons for choosing medical abortion by site, n (%).

	Delhi		Kolkata	
Avoid surgery, instrumentation	295	(73.7)	159	(57.6)
Avoid hospitalization, anesthesia	107	(26.7)	3	(1.1)
Curious, wants to try "abortion pill"	62	(15.5)	8	(2.9)
Safer, fewer complications	13	(3.2)	37	(13.4)
Easier, simpler, better method	48	(12.00)	7	(2.5)
Less pain	15	(3.7)	32	(11.6)
Method recommended	18	(4.5)	16	(5.8)
Convenient, compatible with other duties	22	(5.5)	7	(2.5)
Previous (bad) surgical abortion	0	(0.0)	13	(4.7)
Previous (good) medical abortion	15	(3.7)	4	(1.4)
More private, confidential	12	(3.0)	0	(0.0)

avoid surgery. Many women in Delhi (26.7%) and a few in Kolkata (1.1%) also reported the desire to avoid hospital stay and general anesthesia. Other reasons cited included curiosity about a new method of abortion, a bad previous surgical abortion experience (Kokatta: 4.7%) and earlier favorable medical abortion experience (Delhi: 3.7%; Kolkata: 1.4%).

Compliance and efficacy

Nearly all the women in both sites (Delhi: 95.5%; Kolkata; 97.8%) followed the study protocol exactly, taking misoprostol as scheduled and returning for their follow-up visits (Table 3). When the women did not return for their follow up visits, the clinic staff made diligent efforts to trace them, calling or visiting them at home. Ultimately, 3.7% of the women in Delhi and 2.2% of the women in Kolkata were lost to follow-up (Table 3). Among the 15 women from Delhi and 6 women Kolkata who were lost to follow-up, 12 in Delhi and all in Kolkata had already taken misoprostol. Given concerns about the women lost to follow up having ongoing pregnancies, we reviewed the study forms and available medical records in detail for all these women. In Delhi, while the available information suggested a successful medical abortion in nearly half these cases – an expulsion of the products of conception during their post misoprostol observation period – and failed medical abortion in one such case, for eight women at that site we could not make a preliminary estimation of their medical abortion outcomes. For most of the women lost to follow up in Kolkata, we found evidence of successful medical abortion.

Totally 92.5% of the women with known outcomes in Delhi and 99.3% of such women in Kolkata had successful medical abortions (Table 3). In both the sites, method and user choice contributed equally to the failure rates. In Delhi, however, the rates of ongoing pregnancies (1.6%) and incomplete abortions (1.8%) were higher than in Kolkata, where 0.3% of the women had ongoing pregnancies and none had incomplete abortion. The women in Delhi also requested elective surgical interventions more often than those in Kolkata (Delhi: 2.6%; Kolkata: 0.3%).

Complications and side effects

None of the women experienced any serious complications as a result of their medical abortions.

Table 3. Study outcomes and compliance, by site, n (%).

	Delhi	Kolkata	p-value
Success rate	356 (92.5)	268 (99.3)	<0.001
Failures	29 (7.5)	2 (0.7)	
Method failure			
Ongoing pregnancy at study end	6 (1.6)	1 (0.3)	
Incomplete abortion at study end	7 (1.8)	0 (0.0)	
Medically indicated surgical intervention during study	3 (0.8)	0 (0.0)	
User failure			
Did not take complete therapy	3 (0.8)	00 (0.0)	
Received elective surgical intervention	10 (2.6)	1 (0.3)	
Lost to follow up	15 (3.7)	6 (2.2)	
Evidence of success	6 (1.5)	4 (1.4)	
Evidence of failure	1 (0.2)	0 (0.0)	
No evidence either way	8 (2.0)	2 (0.7)	
Compliance			
Perfect compliers	382 (95.5)	270 (97.8)	
Imperfect compliers	28 (4.5)	6 (2.2)	
Did not take complete therapy	6 (1.5)	0 (0.0)	
Did not return for confirmation of outcome	12 (3.0)	6 (2.2)	

Similarly, no blood transfusions were required. However, three women from Delhi required surgical interventions for heavy bleeding. In addition, a few women also had allergic reactions following misoprostol administration, which consisted of palmar erythema and itching. In all the cases, these reactions were short lived and easily treated with antihistaminics at the study sites.

All the women recorded the side effects they experienced during the study period on a daily symptom diary card (Table 4). As expected, bleeding was nearly universally experienced, with 98.6% of the women in Delhi and 96.7% of the women in Kolkata, reporting some form of vaginal bleeding. On an average, women in Delhi reported 9.1 days of bleeding, while those in Kolkata reported 7.2 days. Most of the bleeding was described to be similar to that or less than that experienced during a normal menstrual cycle. Abdominal cramps was also common in both the sites (Delhi: 59.9%; Kolkata: 61.5%) and generally lasted for about two days. While reports of gastrointestinal side effects – nausea and vomiting – were relatively modest and of short duration in both sites, the women in Kolkata experienced more such side effects and indicated longer durations of such side effects than those in Delhi. This difference was particularly large in the cases of nausea where the rates and duration in Kolkata (experienced: 55.5%; duration: 1.3 days) were twice that in Delhi (experienced: 24.1%; duration: 0.6 days). A small proportion of the women reported fever and chills (Delhi: 11.0%, Kolkata: 17.7%) for less than a day.

Women classified the severity of abdominal cramps using a seven point visual analog scale and on an average, women in both the sites reported moderate pain levels, with an average score of 2.8 in Delhi and 2.5 in Kolkata. The vast majority of women (Delhi: 96.5%, Kolkata: 93.3%), however, indicated that they received adequate pain medication.

We examined additional care required by the women – unscheduled visits or calls made to the study clinics –

Table 4. Women's reports of side effects, by study site.

	Delhi	Kolkata	p-value
Prevalence of side effects, n (%)			
Any bleeding	362 (98.6)	234 (96.7)	0.10
Heavy bleeding	221 (59.1)	125 (47.2)	0.003
Normal bleeding	339 (90.6)	228 (86.0)	0.07
Spotting	274 (73.5)	216 (81.5)	0.02
Nausea	90 (24.1)	147 (55.5)	<0.001
Vomiting	97 (25.9)	93 (35.1)	0.01
Abdominal cramps	224 (59.9)	163 (61.5)	0.68
Fever/chills	41 (11.0)	47 (17.7)	0.01
Mean days of side effects ± SD			
Any bleeding	9.1±3.3	7.2±3.9	<0.0001
Heavy bleeding	2.0±2.6	1.4±2.0	<0.001
Normal bleeding	4.5±2.8	3.5±2.6	<0.0001
Spotting	2.5±2.4	3.5±3.0	<0.0001
Nausea	0.6±1.8	1.3±1.6	<0.0001
Vomiting	0.4±0.9	0.7±1.4	0.006
Abdominal cramps	2.0±2.7	1.9±2.7	0.66
Fever/chills	0.2±0.9	0.4±1.4	0.16
Experiences with pain			
Severity of pain experienced, mean ±SD	2.8±1.3	2.5±1.8	0.03
Received adequate pain medication, n (%)	360 (96.5)	249 (93.3)	0.06

Table 5. Best and worst features of medical abortion, by site, n (%).

	Delhi		Kolkata	
Best features [a]				
None, no reason given	2	(0.5)	5	(1.8)
No surgery, no instrumentation	312	(78.0)	133	(48.2)
Fewer/no side effects	30	(7.5)	108	(39.1)
No hospitalization, no anesthesia	106	(26.5)	1	(0.4)
Convenient, compatible with other duties	31	(7.7)	5	(1.8)
Less anxiety / fear, quick relief	10	(2.5)	21	(7.6)
Safer, fewer problems	7	(1.7)	18	(6.5)
Easy, simple method	23	(5.7)	8	(2.9)
Worst features [a]				
None, no reason given	13	(3.2)	31	(11.2)
Abdominal pain	44	(11.0)	71	(25.7)
Bleeding	97	(24.2)	61	(22.1)
Other side effect(s)	16	(5.0)	27	(11.1)
Procedure takes too long/too many clinic visits/clinic visits too long	18	(4.5)	48	(17.4)
Uncertainty/waiting for expulsion	43	(10.7)	1	(0.4)

[a] Women could give up to two reasons

as an indication of how they managed their side effects and abortion experiences (data not shown). Overall, more women in Delhi than in Kolkata made unscheduled clinic visits (Delhi: 6.5%; Kolkata: 0.4%) or called the clinic hotline (Delhi: 5.7%; Kolkata: 2.5%). While most of the women who made such visits or calls did so only on a single occasion, one woman in Delhi called the clinic three times with concerns about her abortion experience.

Acceptability

Open ended questions were used at the follow up visit to identify the best and worst features of the women's experiences with medical abortion (Table 5). More than three quarters of the women in Delhi (78.0%) and almost half of the women in Kolkata (48.2%) rated avoiding surgery as the best feature of their treatment. A few in Delhi (7.5%) and many in Kolkata (39.1%) appreciated few or no side effects of this method.

When asked about the worst features of their medical abortions, many women complained about the bleeding (Delhi: 24.2%; Kolkata: 22.1%), cramps (Delhi: 11.0%; Kolkata: 25.7%) or other side effects (Delhi: 5.0%; Kolkata: 11.1%) that they had experienced. A few women in Delhi (4.5%) and more in Kolkata (17.4%) rated the long duration of the treatment, multiple visits or prolonged stay in the clinic on the day of misoprostol administration among the worst features of their treatment.

The participants were asked to rate their overall abortion experience as satisfactory, neutral or unsatisfactory. Nearly all the women in both the sites (Delhi: 91.5%; Kolkata: 96.6%) were "very satisfied" or "satisfied" with their abortions. As expected, data not shown found that nearly all the women who rated their treatment as "unsatisfactory" or "very unsatisfactory" had failed medical abortions. Most of the women indicated that they would choose medical abortion again if they needed another abortion (Delhi: 91.5%; Kolkata: 92.9%) and would recommend it to others (Delhi: 91.5%; Kolkata: 94.7%).

Discussion

Our study suggests that a modified abortion regimen consisting of 200 mg mifepristone followed 48 hours later by either oral or sublingual misoprostol in gestations of 56 days or less can be safely, effectively and acceptably provided in day care reproductive health clinics in India. Indeed, non hospital facilities, when given the proper training, can clearly offer medical abortion services in a developing country setting.

In addition to providing further evidence of the safety, efficacy and acceptability of medical abortion in a range of healthcare facilities in India, this study offers additional support for policies that use 200 mg mifepristone and expand gestational age limits. Efficacy rates in both Delhi and Kolkata were as high as or higher than those observed in previous studies in India using a 600 mg dose of mifepristone[10]. With seven Indian pharmaceutical companies currently marketing 600 mg mifepristone for roughly US$21, the regimen approved in India remains out of reach for the vast majority of Indian women. Hence reducing the approved mifepristone dose is likely increase the number of women with access to medical abortion. Similarly, our data further bolsters the case that high efficacy and acceptability rates can be maintained even when gestational age limits are expanded from 49 to 56 days since the last menstrual period. Modifying the current gestational age limit in India would not only bring the DCI approved regimen in line with evidence based practices, but would increase the number of women eligible for medical abortion.

Perhaps most interesting is the fact that the efficacy rate for the Kolkata sites, where misoprostol was administered sublingually, was particularly high at 99.3%. Few studies have reported similarly high efficacy rates, all of which have been among providers with significant medical abortion experience[15-16]. As the providers in Kolkata had no previous medical abortion experience, our results suggest that sublingual administration of misoprostol may have contributed to the high efficacy rate.

The findings of our study should be interpreted in light of the following limitations. Though women using sublingual misoprostol in our study had a higher efficacy than those using oral misoprostol, this cannot be used as an evidence of higher efficacy of sublingual misoprostol as the study was not designed to compare outcomes across the oral and sublingual route of administration. A well designed randomized controlled trial is needed to assess whether sublingual misoprostol in indeed more effective than oral misoprostol for early abortion following mifepristone. Furthermore, our study was conducted in two large cities in India and the findings may not reflect the situation in semi urban or rural settings where need for safe abortion services is particularly acute. Additionally our findings may underestimate the true failure rate of medical abortion as we could not confirm outcomes in several women who were lost to follow up. We do not expect this bias to affect our findings substantially, as we were able to estimate the possible outcome in a large number of women who were lost to follow up. In Kolkata, we were reasonably able to estimate the possible abortion outcome in all but two women. In Delhi we did not have sufficient evidence to estimate the possible outcome in more than half (8 of 15 women) of the women lost to follow up. Even if all of these women received surgical interventions in non study hospitals/clinics, the efficacy of medical abortion in Delhi clinics would only decrease to 90.0% from our current finding of 92.5%.

Though rare, a patient may experience moderate to severe vaginal bleeding at home after the drug administration and hence the patients need to be properly counselled and adequate emergency management for the same be readily available at the clinic.

In India, researchers should continue to examine early medical abortion provision in a range of healthcare settings including in rural health care centers, thereby expanding access to safe abortion. Studies examining provision of medical abortion by nurses and other mid level providers are also critical, as are carefully designed and user friendly provider training and patient information materials.

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