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Review article

Flexible mifepristone and misoprostol administration interval for first-trimester medical termination☆

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Abstract

Background: The administration interval between mifepristone and misoprostol is usually about 36–48 h, which might affect a woman's choice of method of termination. Unwanted outcomes such as uterine bleeding, painful cramps and psychosocial issues which may occur during this long interval can be altered by a shorter administration interval. A shorter interval will be cost-effective as it saves both women's and clinician's time and other resources. If the waiting time interval between therapeutic interventions could be reduced without compromising efficacy, it will potentially improve compliance, patient acceptability and quality of care.
Study design: A systematic review of randomized controlled trials published from 1999 to 2008 was conducted to assess the evidence for a shorter mifepristone and misoprostol administration interval at first trimester medical termination. Searching strategy included MEDLINE, EMBASE, CLINAHL and Cochrane Library. The primary outcome measure was complete abortion without the need for a surgical procedure.
Results: Five randomized controlled trials (RCT) compared the efficacy of mifepristone and misoprostol administration intervals between 0 and 72 h in 5139 participants. The complete abortion rates varied between 90% and 98%. Although the meta-analysis of pooled data of all RCTs shows no statistically significant difference in efficacy between the shorter and longer dosing intervals, there is a trend toward slightly lower success rates with administration intervals earlier than 8 h.
Conclusions: Overall efficacy of complete abortion is not statistically different between the longer and shorter administration intervals. This might encourage the clinician to adopt a 'flexible policy' with fully informed consent and consideration of all circumstances.

Keywords: Medical abortion; Pregnancy termination; Mifepristone; Misoprostol; Time interval

1. Introduction

Surgical abortion up to 9 weeks of gestation has been the method of choice for elective pregnancy termination since the 1960s. Medical termination became an alternative method for first trimester terminations with the availability of prostaglandins in the 1970s and a progesterone receptor agonist, mifepristone, in the 1980s. Various medical termination techniques have evolved over the past two decades based on the clinical studies. The aim of this review is to evaluate studies which investigated different time intervals between administration of misoprostol and mifepristone.

The efficacy of the early medical abortion regimen consisting of mifepristone and misoprostol is well known [1–3]. This regimen usually involves administering misoprostol 36-48 h following oral administration of mifepristone [2].

The relatively long interval between administration of the two agents might affect a woman's choice of method of termination since some women would prefer a less time-consuming process [4,5]. Rarely, women change their mind after taking mifepristone during this long wait, which might lead to various problematic issues. Additionally, women often experience uterine bleeding and painful cramps during this "interval" [6–10]. These undesirable adverse effects of mifepristone can be bypassed by shortening the misoprostol administration interval. The simultaneous administration would improve drug compliance. Most importantly, a short

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interval will be cost-effective as it saves both women's and clinician's time and other resources.

Mifepristone, a synthetic antiprogestogen, acts by competitively blocking the progesterone receptor which is necessary to maintain the pregnancy. Mifepristone has 2.5–5 times higher affinity for the progesterone receptor than progesterone. Mifepristone also increases uterine contractility, and most importantly, it sensitizes the myometrium to prostaglandins [10,11]. Mifepristone as well as its metabolites are antagonists to progesterone binding to its receptor. When mifepristone 200 mg is administered orally, it is rapidly absorbed and reaches peak plasma concentration in 1-2 h. Thereafter, its concentration decreases slowly with mean elimination half life of 24 h [12]. Although enteral absorption is as high as 70%, the bioavailability of this agent reduced to 40% due to first-pass metabolism by the liver [10,12,13].

Pharmacokinetic studies of misoprostol have shown that vaginally administered misoprostol takes a long time (70–80 min) to reach its peak plasma concentration which decreases slowly with detectable levels present after 6 h, in comparison to oral administration. Plasma concentrations of orally administered misoprostol peak in approximately 12–20 min and decline rapidly thereafter with a terminal half life of 20–40 min [10,14]. Moreover, the bioavailability of vaginally administered misoprostol is three times higher [2,10] than the oral route.

If the waiting time interval between therapeutic interventions could be reduced without compromising efficacy, it would improve compliance [15], patient acceptability [4], and quality of care.

2. Methods

A systematic review by Schaff [16] revised evidence of five randomized medical abortion trials including 4793 participants, published from 1999 to 2004. The present review is an expansion of Schaff's systematic review including data up to December 2008.

A systematic search strategy included MEDLINE, EMBASE, CINAHL and Cochrane Library were used to recognize the randomized controlled trials (RCTs) comparing different mifepristone and misoprostol regimens focused on the time interval between mifepristone and misoprostol when given to induce at first trimester medical terminations of pregnancy. All routes of misoprostol administration were included. The combination of medical subject headings "*mifepristone*," "*misoprostol*," "*abortion*," "*termination*," "*interval*," "*concurrent*," and "*simultaneous*" were combined using the Boolean operators "or" and "and" as appropriate using the searching engine of the [United Kingdom's] National Health Service Evidence Health Information Resources [17]. Relevant studies were also sought manually in the reference lists of primary papers and reviews. Two independent reviews have been carried out. Each abstract was screened for relevance and the full text acquired if determined to be relevant. Only RCTs published in the English language have been included. The review includes studies published from January 1999 to December 2008.

The primary outcome was a complete abortion not requiring surgical procedure. Statistical analysis was performed using the software Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ (2005).

3. Results

A total of five, good quality randomised clinical trials were identified (Table 1) from 155 publications retrieved by the literature search.

Participants within the Creinin et al. [18] study were given mifepristone 200 mg orally and were then randomized to self-administer misoprostol intravaginally immediately in the clinic (group 1) or 24 h later at home (Group 2). One thousand one hundred women returned for an evaluation, including transvaginal ultrasonography, 7±1 days after randomization. Women who had not aborted were offered a second dose of misoprostol and returned for another evaluation in approximately 1 week. If a suction aspiration was performed for any indication, the treatment was considered a failure. The complete abortion rate of group 1 95% (95% CI 93.0–96.8%) was statistically non-inferior to that for Group 2 96.9% (95% CI 95.1–98.2%) (p=.003). Adverse effects were almost the same. The relative risk of failed abortion was 1.59 (95% CI 0.86-2.96).

Guest et al. [4] conducted a two-arm, parallel, open RCT in a medical termination service in a UK teaching hospital. Eligible women were randomized to receive mifepristone 200 mg orally followed by vaginal misoprostol 800 mcg either 6 h (n=225) or 36–48 h (n=225) later. Women randomized to 6 h group were allowed home immediately after receiving vaginal misoprostol, whereas women in the 36-48 h group were admitted for 4-6 h, before they were discharged home. The primary outcome measure was successful termination, defined as either the absence of gestational sac on first ultrasound scan performed between 2nd and 7th day after mifepristone or no requirement of further surgical intervention. The data was analyzed primarily on an intention-to-treat basis and comparison of continues, non-normally distributed data was performed with the nonparametric Mann–Whitney U test. Continuous variables were expressed as a mean and standard deviation or medians and interquartile range. The overall successful termination rate, not requiring surgical evacuation, in the 6-h regimen was 90% (189/210) compared with 96% (207/215) in the 36–48-h regimen. The p value of this difference has not reported. The relative risk of failed abortion was 2.87 (95% CI 1.24–6.65). Thirteen (6%) participants in the 6 h group and 59 (27%) in the 36-48 h group failed to attend the initial follow-up ultrasound scan and no women required a