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Mifepristone and misoprostol for cervical ripening in surgical abortion between 12 and 14 weeks of gestation: a randomized controlled trial

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ABSTRACT

Objective: Misoprostol and mifepristone are the two substances recommended for cervical preparation during first-trimester surgical abortions to decrease intraoperative bleeding and complications. The objective of the study was to evaluate whether the combination of mifepristone and misoprostol for cervical preparation in an elective surgical abortion between 12 and 14 weeks of gestation can reduce blood loss in comparison to misoprostol or mifepristone alone.

Study design: A randomized controlled trial was performed in Marseille, France between May 2013 and May 2014. Women requesting a surgical abortion under general anesthesia between 12 and 14 weeks of gestation were 198, randomized into three groups: one received 400 μg oral misoprostol 3 h before surgery, one 200 mg oral mifepristone 36 h before surgery, and the other, both treatments. The main outcome was the quantity of intraoperative bleeding. The secondary outcomes were duration of intervention, ease of dilatation, and complications.

Results: The quantity of intraoperative bleeding differed significantly between the groups ($p = 0.001$): 222 ± 64 mL in the combination group, 329 ± 129 mL in the misoprostol group, and 276 ± 119 mL in the mifepristone group. The combination was associated with a shorter operative duration ($p = 0.001$): 5 ± 2 min in the combination group, 7 ± 5 min in the misoprostol group, and 7 ± 3 min in the mifepristone group. A hemorrhage was observed for 5 of 55 women (9%) in the combination group, 13 of 51 (25%) in the misoprostol group, and 9 of 56 (16%) in the mifepristone group ($p = 0.08$). No cervical laceration or uterine perforation was reported.

Conclusions: The combination of mifepristone and misoprostol in cervical preparation for elective surgical abortions between 12 and 14 weeks of gestation significantly reduced blood loss in comparison to misoprostol or mifepristone alone.

Introduction

Elective abortions are an international public health issue, with one in five pregnancies worldwide resulting in the decision to terminate [1]. In 2008, 43.8 million elective abortions were performed worldwide, for a mean of 28 per 1000 women aged 15–44 years, with nearly 8.5 million complications [1]. These complications can be life-threatening and are responsible for 13% of the annual international maternal mortality [1]. Surgical abortion requires mechanical dilatation of the uterine cervix. This cervical dilatation is the source of the principal complications of abortions: cervical laceration (0.1–0.6%), uterine perforation (0.1–2.3%), including the risk of wounding adjoining organs (bladder, vessels, or rectum), severe hemorrhage (0.1–0.4%), and finally the long-term risks of cervical incompetence, late miscarriage, and preterm delivery [2–5]. On the other hand, inadequate cervical dilatation at the moment of aspiration can cause other short-term complications: ongoing pregnancy and infection that can affect fertility [2]. Cervical preparation has shown benefits in terms of cervical dilatation and reduction of intraoperative bleeding, as well as a reduction in the incidence of complications [6–9]. Misoprostol and mifepristone are the two substances recommended for cervical preparation during the first trimester [6–13]. Nonetheless, the benefit of combining both drugs during the first trimester has not been assessed.

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The primary objective of this study was to compare the effectiveness, assessed by intraoperative blood loss, of misoprostol, mifepristone, and the combination of the two treatments, in cervical preparation for elective surgical abortions between 12 and 14 weeks of gestation. The secondary objectives were to compare the 3 treatment strategies in terms of duration of intervention, ease of dilatation, satisfaction regarding the procedure, women's anxiety and perioperative experience, and complications.

Materials and methods

This study was a single-center randomized, controlled, single (physician)-blinded trial conducted at the Conception University Hospital Centre in Marseille in France, in 3 parallel groups: the combination group, receiving a combination of mifepristone and misoprostol, the misoprostol group, and the mifepristone group.

The inclusion criteria were: women aged 18 years or older, requesting an elective abortion under general anesthesia for an intrauterine singleton pregnancy between 12 and 14 weeks of gestation (from last menstrual period) on the procedure date and who provided written informed consent.

The exclusion criteria were women with a uterine malformation, coagulation disorders defined by laboratory indicators (prothrombin time <70%, patient/control ratio for activated clotting time >1.20), known allergy or hypersensitivity to one of the active substances or excipients of either mifepristone or misoprostol or a contraindication to its use, lack of health insurance (in accordance with the French law), or refusal to provide informed consent.

Secondary exclusion criteria were: failure to perform the intervention (continuing the pregnancy, spontaneous abortion before taking the medication), and inability to receive general anesthesia the day of the abortion (not fasting, desire to change anesthesia modality, and an intercurrent disease).

Pregnancies were dated by ultrasound measurement of the craniocaudal length according to the French guidelines. It was expected to range between 55 and 84 mm on the day of the abortion [14].

Computer-generated randomized lists were drawn up before the beginning of the study with a permuted randomization scheme (block size: 6, randomization ratio [1:1:1]). After the written consent was signed, women were randomly assigned to one of the 3 treatment groups. To ensure blinding, the treating medical staff and investigators were unaware of the allocation. Only the pharmacist delivering the treatments and the women knew the allocation.

In the combination group, patients were given 200 mg of oral mifepristone to take 36 h before the procedure, and 400 μg of oral misoprostol to take 3 h before the procedure. Women in the misoprostol group received 400 μg of oral misoprostol to take 3 h before the procedure, and those in the mifepristone group 200 mg of oral mifepristone to take 36 h before the procedure.

The abortion was performed under general anesthesia according to standard clinical practice at this gestational age. After asepsis of the vulva and vagina, the operator used a Pozzi tenaculum to grasp the cervix and measure the spontaneous cervical dilatation. Supplemental mechanical cervical dilatation was then performed with Hegar dilators, with the size increasing in increments of 0.5 mm, up to dilator number 14 when possible. The amniotic sac was systematically breakthrough with the last dilator, so as to let out the amniotic fluid. The aspiration then took place, with a cannula of the corresponding diameter. Five experienced surgeons performed all abortions. Women were monitored for 6 h, first in the recovery room and then in the department.

The primary endpoint was the quantity of intraoperative bleeding. It is the quantity of blood collected during the intrauterine aspiration, beginning after the mechanical cervical dilatation and ending with the withdrawal of the cannula at the end of the procedure. It was collected into a graduated (every 50 mL up to 1 L) aspiration collection box. At the end of each procedure, the surgeon who performed it read and recorded the quantity of blood in the box, expressed in mL.

The duration of the intervention was defined as the time from the beginning of the supplemental mechanical cervical dilatation to the end of the intrauterine aspiration. The spontaneous cervical dilatation was assessed by the diameter of the Hegar dilator that entered the cervix without force, before the supplemental mechanical cervical dilatation began. The procedure was standardized by attempting to use the n°14 Hegar dilator and continuing with gradually decreasing dilators. The maximum cervical dilatation was the largest diameter of Hegar dilator introduced at the end of the mechanical dilatation, with a maximum of 14 mm.

The ease of this supplemental mechanical cervical dilatation was assessed by the operator with a visual analog scale (VAS) ranging from 0 (very difficult) to 10 (very easy).

The satisfaction regarding the procedure was assessed separately by a VAS by the physician and by the woman before discharge (0–10, with a higher score corresponding to greater satisfaction).

Anxiety was assessed with the State-Trait Anxiety Inventory (STAI) before and after the intervention. The STAI is a self-administered questionnaire, developed by Spielberger and validated in French; it comprises 20 questions that assess the subject's emotional state [15,16]. The scale range is 20–80, with higher scores representing higher levels of anxiety.

Perioperative experience and satisfaction during the perioperative period for general anesthesia was assessed with a well-validated self-administered questionnaire, the EVAN-G, which consists of 26 patient-generated items that yield a global index (score range, 0–100, worst possible experience to best possible experience) [17–19].

Tolerance of the treatments was assessed by questioning the women about side effects before the procedure began.

The intraoperative complications reported were: cervical lacerations (lesion of the cervix requiring a suture for hemostasis or reconstruction of the cervical anatomy), uterine perforation (diagnosis established by intraoperative ultrasound or instrumental assessment), hemorrhage between the end of aspiration and hospital discharge (defined as of intermediate severity if it was necessary to repeat the aspiration or inject oxytocin, and severe if a blood transfusion or hemostatic surgical procedure was required — either hysterectomy or artery ligation).

Assumptions for the sample-size calculation were based on an analysis of the medical records of the study center (in 2012). The sample size was determined to obtain 80% power and 5% significance level to detect 30% difference (considered as the minimal clinically significant difference) of quantity of blood loss for pair-wise comparisons of groups. Considering a standard deviation maximizing the sample size (i.e., 150 mL) and a 1:1:1 ratio, the calculation showed that 189 women were needed (63 per group). Assuming a potential dropout rate of 5%, we planned to include 198 women.

In compliance with the applicable legislation, the National Agency of Drug Safety (ANSM) and the Patient Protection Committee (CPP) of the South-Mediterranean region approved this study in February 2013.

Data analysis

Results are reported according to the CONSORT statement [20,21]. SPSS version 17.0 software was used for data analysis.