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Treatment of uterine myoma with 5 or 10 mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial

Josep Ll. Carbonell Esteve [a,*], Rita Acosta [b], Yasmiriam Pérez [b], Rosa Campos [b], Aleta Valle Hernández [b], Carlos Sánchez Texidó [b]

[a] *Mediterránea Médica Clinic, Valencia, Castelló, Valencian Country, Spain*
[b] *"Eusebio Hernández" Gynecology and Obstetrics Teaching Hospital, Havana, Cuba*

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ABSTRACT

Objectives: To evaluate the efficacy and safety of 5 and 10 mg doses of mifepristone for 6 months for the treatment of uterine fibroids and to check those results at 1 year post-treatment.
Study design: Randomised double-blind clinical study carried out at the "Eusebio Hernández" Hospital, Havana, Cuba. One hundred and seventy-six women with symptomatic uterine fibroids received one daily capsule of 10 mg mifepristone orally or one daily capsule of 5 mg mifepristone orally, over 6 months. Up to two endometrial biopsies were performed. Reduction in fibroid volume was used to evaluate efficacy.
Results: The 5 and 10 mg dose had a similar efficacy in reducing the fibroid volume, 48.1% and 39.1%, $p = 0.07$, and that of the uterus, 30.3% and 27.2%, $p = 0.63$, respectively. Twelve months after treatment the majority of the subjects were asymptomatic with symptom prevalence similar to that at the end of treatment, except for hypermenorrhea and metrorrhagia, although the intensity of hypermenorrhea was much less, $p < 0.01$.
Conclusions: (1) Both doses obtain similar results in reducing fibroid size. (2) Administering 6 months' treatment achieves symptomatic improvement lasting 1 year in a high percentage of cases. (3) More studies need to be carried out with longer treatment and follow-up periods.

1. Introduction

Almost half of women between 36 and 49 years of age have a uterine fibroid and many of them present with heavy bleeding causing iron-deficiency anaemia, which results in many cases in hysterectomy [1–4]. Classic medical treatment with progesterone, danazol, gestrinone and GnRH agonists has been somewhat disappointing [5–7]. The progesterone receptor modulators (PRMs) make up an interesting group of compounds, potentially useful in various gynaecological conditions such as dysfunctional hemorrhage, uterine fibroids and endometriosis. Ulipristal (CDB 2914) and ProelLex (CDB 4124) have also shown their usefulness in this respect [8–10], but it is the oldest of all the PRMs, the almost pure antagonist of the progesterone receptors, mifepristone, that has been the focus of most studies [11–20].

Endometrial thickening, a feature of long-term mifepristone treatment, is not measured in these studies. This point is one of the main drawbacks of mifepristone since it has recently been shown that long-term treatment with this or other PRMs does not produce, as was formerly thought, simple hyperplasia but rather benign histological endometrial modifications that a North American group of experts has grouped together as PRM-associated endometrial changes (PAECs) [13,21–23].

The primary aim of this study is to evaluate the efficacy and safety of 10 mg versus 5 mg mifepristone daily for 6 months in the treatment of uterine fibroids. A secondary aim was to monitor those results for 1 year after treatment.

2. Materials and methods

2.1. Design

This double-blind randomised clinical trial with two treatment groups was approved by the Scientific Committee of the "Eusebio Hernández" Gynaecology and Obstetrics Teaching Hospital. Subjects were recruited from the gynaecological hospital classification consultancy and primary health care units. The clinical trial was carried out in accordance with the revised version of the Helsinki Declaration and with the standards of Good Clinical Practice. The

* Corresponding author at: Clínica Mediterrania Medica, C/ Salvador Guinot, 14, Valencia 46017, Spain. Tel.: +34 96 358 6020; fax: +34 96 3785485.
E-mail addresses: schja@infomed.sld.cu, josepcarbon@yahoo.es (J.L.C. Esteve).

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study began in May 2008 and the last subject included was evaluated in October 2010, 12 months after termination of treatment with mifepristone.

2.2. Subjects

Women volunteers, 18 years old or older, with uterine fibroids were eligible for the study. Inclusion criteria were: (a) symptomatic uterine fibroids, (b) fertile age, (c) use of non-hormonal contraceptive method such as condoms, copper IUD, diaphragm, etc., during the whole treatment period, (d) monthly record of all vaginal bleeding and of mifepristone side effects, (e) agreeing to at least two endometrial biopsies being performed. Exclusion criteria were: (a) pregnancy or wish to become pregnant, (b) breastfeeding, (c) hormonal contraception or any hormonal therapy received in the last 3 months, (d) signs or symptoms of pelvic inflammation, (e) adnexal masses, (f) abnormal or unexplained uterine bleeding, (g) suspicion or diagnosis of malignant neoplasm, (h) signs or symptoms of mental illness, (i) adrenal disease, (j) sickle-cell disease, (k) hepatic disease (l) renal disease, and (m) contraindications to anti-progesterone.

2.3. Treatment

Group I: one 10 mg capsule of mifepristone per day taken orally over 6 months. Group II: one 5 mg capsule of mifepristone per day taken orally over 6 months. The mifepristone was supplied by ZIZHU PHARM Laboratory, Co. Ltd., Beijing, China. L. Amigó Pharmacy, Valencia, Spain prepared the 5 and 10 mg mifepristone capsules, and they were identical in appearance, size, shape and colour: they could only be distinguished by a code that was opened once the study was over. Treatment did not begin on the first or second day of menstruation but chronologically as patients joined the study, regardless of where they were in their menstrual cycle.

2.4. Examinations performed

Complete gynaecological examination and abdominal or vaginal ultrasound of the uterus was performed before the start of the study, again 3 and 6 months into treatment and 3, 6, 9 and 12 months after termination. Fibroid volume was calculated using the formula: $4\Pi abc/3$ where a, b and c are the radii of the spheres in each of the three planes and are expressed in cubic centimetres [24]. If the subject had more than one myoma, the measurement of the biggest was taken and its variations were used to evaluate efficacy. The total volume of the uterus was measured using the previously mentioned formula. Ultrasonography was used to calculate endometrial thickness in mm. All ultrasound data were obtained with ALOKA Co. Ltd. Ultrasound Diagnostic Equipment SSD-4000, Mitaka-SHI, Tokyo, Japan and two doctors specializing in ultrasound carried out the measurements.

Blood samples were taken for hematological and hepatic tests every 3 months during treatment. It was decided beforehand that any subject presenting alterations in transaminases three times or more above their normal maximum limit, in line with FDA recommendations, would be dropped from the study (Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, US Department of Health and Human Services, July 2009).

As a safety step, endometrial biopsy was performed: (1) prior to treatment if any of the following criteria applied: (a) endometrial thickness $>$ 8 mm; (b) episodes of vaginal bleeding lasting more than 10 days, (c) vaginal bleeding during the 3 weeks prior to onset of menstruation, (d) copious vaginal bleeding; (2) 3 months during treatment if the endometrial thickness was greater than 8 mm; and (3) at the end of treatment on all subjects except those who had had one at 3 months and it was only repeated on those whose endometrial thickness at 6 months was greater than 8 mm. Our team of pathologists decided to carry out a triple-blind reinterpretation of all the biopsy samples.

2.5. Follow-up visits and evaluation

Once treatment was over the subjects were seen 3, 6, 9 and 12 months later. During the follow-up period no other treatment or placebo was administered that might obscure the fibroid evolution or symptoms and thus any chance of a placebo effect as a possible explication of an improvement sustained in the prevalence of symptoms was eliminated.

2.6. Evaluation of efficacy

The main variable to evaluate efficacy was the percentage change in fibroid volume at 6 months into treatment and 12 months after its termination. Secondary variables used to estimate efficacy were: (a) percentage change in the uterus volume, (b) changes in prevalence of symptoms of the myoma: pelvic pain, lumbar pain, rectal pain, pelvic pressure, urinary symptoms, dyspareunia, hypermenorrhea and metrorrhagia, (c) pelvic pain and hypermenorrhea intensities were evaluated by a visual analogue scale (VAS) from 0 to 10 where 0 represented absence of symptoms and 10 their maximum value and was indicated by the patient herself. All these variables were measured in each of the study evaluation periods.

2.7. Evaluation of safety

The main variables to evaluate safety were the frequency of PAECs or simple hyperplasia. Other variables to evaluate safety were: (a) changes in endometrial thickness measured by ultrasound (mm), (b) mifepristone side-effects: amenorrhea, hot flushes, nausea, dizziness, vomiting, fatigue/tiredness, (c) changes in hepatic transaminase levels evaluated every 3 months up to end of treatment.

2.8. Number of patients to be included

The expected reduction in fibroid volume was used to estimate the size of the study sample. We assumed that in a 6 months treatment period 10-mg mifepristone doses would provide 50% reduction of the fibroid size and that 5-mg mifepristone doses would give 30% reduction of the fibroid volume, with regard to the pre-treatment volume in both cases. The calculations performed with GPower 3.0.10 (Windows Software) indicated that with 74 subjects in each treatment group (148 for the entire study) it was possible to detect such 20% difference between the two mifepristone doses groups with a type I = 5% and with a power of 80% [25]. The study sample size was increased by 13% (85 patients in each group, for a total of 170 in the whole study), so as to offset subject loss over the course of the mifepristone treatment.

2.9. Assignment to treatment groups

The subjects were assigned to one or the other treatment groups at random according to the order of the assignment list drawn up by a computer and this was carried out as follows: once the subject had been evaluated in line with the inclusion and exclusion criteria and had signed the Informed Consent, the envelope corresponding to the subject's numbered incorporation into the study was opened and she was included in the treatment group indicated on the card contained in the envelope: "mifepristone A" or "mifepristone B" where A corresponded to one of mifepristone doses used in the study and B to the other.