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Original Article

Mifepristone 2.5, 5, 10 mg versus placebo in the treatment of endometriosis

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ABSTRACT

Objectives: To evaluate the effectiveness and safety of 2.5, 5 and 10 mg doses of mifepristone against a placebo in women with laparoscopic diagnostic of endometriosis.
Methods: Double-blind, placebo-controlled study of 360 subjects randomly assigned to receive orally one daily tablet of 2.5, 5 or 10 mg mifepristone for 6 month, or 1 daily tablet of mifepristone placebo for 3 months, (90 in each treatment group), carried out at "Eusebio Hernández" Hospital, Havana, Cuba. Efficacy was assessed by measuring changes in prevalence of dysmenorrhea and changes in scores according to AFS. Safety was evaluated by the incidence of hot flushes, nausea, dizzy spells, vomiting, fatigue/tiredness, raised hepatic transaminases, histological alterations of the endometrium.
Results: In the mifepristone groups, the prevalence of symptoms was significantly inferior to those at the beginning of treatment with no significant differences between the groups of 5 and 10 mg, unlike in 2.5 mg of mifepristone and the placebo group. The scores of the AFS were significantly different at the end of the treatment in the mifepristone groups. In the mifepristone groups, there were 9/264 (3.4%) subjects with raised hepatic transaminases up to 99 IU.
Conclusions: Mifepristone 5 mg was safer and more effective than the other mifepristone doses and placebo.
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1. Introduction

Endometriosis, characterized by the ectopic presence of endometrial-like glands and stroma, is a common gynecological condition with an enigmatic pathogenesis.[1] There is currently no cure for endometriosis and reported recurrence rates after surgical therapy are high.[2] Approved treatments for endometriosis include hormonal therapies.[3] These methods of treatment are relatively effective but their side-effects limit their effectiveness and impeding their continued use.[4–6]

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The progestagen dienogest has shown to be more efficacious than placebo in relieving pain associated to endometriosis and also showed a similar efficacy to GnRh in alleviating endometriosis main symptom.[7]

Bouchard et al. reported that selective progesterone receptors modulators (SPRM), as mifepristone and progestagens, could reduce the growth of endometrial tissue and also diminish endometriosis associated pain.[8]

In contrast, Brown et al. concluded that it could only be present a limited evidence to support that the use of progestagens and antiprogestagens (gestrinone) relieves endometriosis associated pain. But, they warned that the reviewed studies are few with a scarce number of subjects, and then, that conclusion is not definitive.[9] Brown et al., only analyze the antiprogestagen gestrinone; in their revision, they did not make any reference to the studies by Kettel et al., Murphy et al., where they treated endometriosis with mifepristone.[10–13]

Agreeing with Bouchard et al., Prentice et al. concluded that also progestagens and the antiprogestagens gestrinone ameliorate the pain symptoms associated to endometriosis.[3]

SPRMs, in general, own an antiproliferative effect, as that has been pointed out that it happens in the endometrium of primates,[14] and in rodent mammary tumors.[15]

Mifepristone is a practically pure SPRM, which its strong antiprogestagenic action is only overtaken by onapristone. Mifepristone acts being coupled to the progesterone receptors at uterine cervix level, in the endometrium, miometrio, mammary tissue, and in every site where progesterone receptors exist.

Endometriosis is considered an estrogen-dependent condition influenced by the levels of aromatase activity, whose production is markedly increased in the ectopic endometriosis implants compared with eutopic endometrium and this leads to an increase in the production of estradiol.[16] Mifepristone blocks medroxyprogesterone acetate induced aromatase action in the endometrial cells.[17]

A study on Wistar rats using a mifepristone implant proved to be effective on endometriotic lesions.[18] Several studies published by Kettel et al. using 100, 50 and 5 mg mifepristone to treat endometriosis obtained significant reductions of pain (intensity and prevalence) and also in the dimensions of the endometriotic lesions according to the mifepristone dose used.[10–13]

In 2010, we carried out a pilot study using mifepristone 5 and 25 mg doses for the treatment of endometriosis. The 5 mg dose had a similar action to that of the 25 mg regarding clinical improvement: reducing pain in 95% of cases and reducing in more than 50% the volumes of the endometriotic lesions according to AFS scores.[19]

In China, during the past decade, more than a hundred clinical trials were carried out including several thousands of patients using mifepristone for the treatment of endometriosis, though Sun-Wei Guo questions their results because of inappropriate protocol designs.[20]

The fact that our results confirmed, or were better than the ones reported by Kettel et al., using 5 mg-mifepristone doses led us to design a clinical study trying to get a more definitely result on the use of mifepristone to treat endometriosis.

The objective of this study was to evaluate the effectiveness and safety of doses of 2.5, 5 and 10 mg mifepristone versus a placebo for the treatment of endometriosis.

2. Materials and methods

This is a double-blind randomized clinical trial, with 3 mifepristone treatment groups and one placebo group to evaluate efficacy and safety in the treatment of endometriosis. The study was approved by the Ethics and Science Committee at the ''Eusebio Hernández'' teaching hospital in Havana, Cuba and carried out in accordance with the Declaration of the XVIII and XLI World Medical Assembly of Helsinki (1964) and last modified by the Tokyo Assembly (2004). At the recruitment visit, subjects were informed the pros and cons and possible side-effects of the treatment.

2.1. *Examinations undertaken*

Before treatment, for all patients, thorough gynecological and pelvic ultrasound examinations for endometrioma and diagnostic laparoscopy were performed to determine localization, extent and severity of the endometriotic lesions; a score was assigned according to the revised American Fertility Society (AFS) classification.[21] Blood samples were taken for hematological tests and hepatic function. Before treatment, endometrial biopsy was performed if endometrial thickness, measured at any moment of the menstrual cycle, by ultrasound was >8 mm or if an abnormal bleeding had occurred in the past 3 months. At 90 and 180 days of treatment ultrasound examination for endometrioma of the pelvis was undertaken; when treatment ended, a diagnostic-therapeutic laparoscopy and endometrial biopsy were performed. All our operators are more than sufficiently trained in gynecological investigation, both on ultrasonography or surgical techniques; they were blinded to the experimental protocol.

2.2. *Subjects*

Women with laparoscopic confirmed endometriosis who volunteered to take part in the study. Inclusion criteria: a) age 18 to 45, b) patients with dysmenorrhea or pelvic pain not attributable to other gynecological illness and c) acceptance of using barrier contraceptive methods during treatment. Exclusion criteria: a) breastfeeding, b) hormonal or surgical therapies less than 4 months previous to study, c) diabetes, d) severe arterial hypertension, e) hepatopathy, renal malfunction, endocrinopathy, and f) any contraindication about the use of antiprogestins.

2.3. *Products used*

The mifepristone was supplied by Zizu Pharma Laboratories, Beijing, China for the first 91 subjects, and by Litaphar Laboratories, Azpeitía, (Guipúzcoa, Basque Country), Spain for patients 92 to 360.

2.4. *Treatment*

Group I: 2.5 mg mifepristone per day for 6 months; Group II: 5 mg mifepristone per day for 6 months; Group III: 10 mg mifepristone per day for 6 months; and Group IV: a mifepristone placebo daily for 3 months were followed. The mifepristone was