The Usefulness of Medroxy-Progesterone Acetate for Genital Spotting after the First Injection of GnRH Agonist Treatment for Endometriosis

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Abstract: The best treatment for endometriosis remains gonadotropin-releasing hormone (GnRH) agonist. However, most patients complain of genital spotting during the first month after the injection of GnRH agonist, a distressful side effect of treatment with GnRH agonist for endometriosis. Therefore, we investigated the effect of 10mg daily medroxy-progesterone acetate (MPA) for seven (group 1) or 14 days (group 2) for genital spotting.

We observed the discontinuation of genital spotting and compared the days from medication administration to the discontinuation of genital spotting between the two groups.

(1) In all patients, genital spotting stopped 5–7 days after MPA treatment ($p < 0.01$).

(2) There was no statistically significant difference in the number of days until discontinuation of genital spotting after 10 mg MPA treatment between the two groups (p = nonspecific).

(3) There was no recurrence of genital spotting in either group during six months of GnRH agonist treatment.

Therefore, genital spotting during the first month following the injection of GnRH agonist was effectively managed with seven days of 10mg/day MPA. This proved to be a very useful treatment method for genital spotting during the first month after the injection of GnRH agonist.

Keywords: Endometriosis, Gonadotropin-releasing hormone agonist, Medroxy-progesterone acetate, Genital spotting.

INTRODUCTION

Endometriosis occurs in 6 – 20 % of reproductive age women [1] and induces symptoms, such as dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility. The pain related to endometriosis does not correlate with the degree of disease and the pain severity and response to medical treatment vary considerably between individuals.

Medical treatment for endometriosis-related pain includes anti-estrogenic medications, such as progestogen and danazole, medications that induce a temporary pseudo-menopausal state, such as gonadotropin-releasing hormone (GnRH) agonist, and oral contraceptives that induce a pseudo-pregnancy state [2]. Recently, aromatase inhibitors have been studied for the treatment of pain symptoms associated with endometriosis [3, 4]. High dose progestogen is known to be very effective for endometriosis-related pain and medroxy-progesterone acetate (MPA, Provera®) is a typical medication. MPA suppresses the release of gonadotropin from the pituitary, which induces anovulation and lowers serum estrogen levels. MPA acts directly on the progesterone and androgen receptors in the endometriosis lesion, causing atrophy by inducing decidualization of the endometrial tissue. High dose MPA treatment (100mg/day) lowers the level of sex hormone-binding globulin (SHBG) and raises the level of free androgen. Luciano *et al*. [5] reported a significant decrease in American Fertility Society (AFS) score by the use of MPA (50 mg/day) in endometriosis patients. Despite this impressive effect, oral high dose MPA has many complications, including abnormal bleeding, weight gain, body fluid retention, and breast pain, which can lead patients to discontinue the medication. Recently, dienogest, which has both a 19-norprogestin effect and a progesterone derivative effect that acts locally on uterine endometrial tissue, has been introduced as an effective endometriosis treatment method [6]. Kohler *et al*. were the first to introduce dienogest for the treatment of endometriosis in 1987 [7]. Dienogest has no androgenic effects and low hypo-estrogenic effects and has been shown to be safe and effective in endometriosis treatment [8].

As mentioned above, several medicines have been developed for endometriosis-related pain, but the most commonly used medications are GnRH agonists, such

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as leuprolide acetate, which induce a temporary pseudo-menopausal state. GnRH agonists cause an estrogen deficiency, leading to severe complications, such as facial flushing, vaginal dryness, headache, and decreased libido. Moreover, because it decreases bone density, its treatment period is limited to no more than six months. To overcome this limitation, add-back therapy with a low dose of estrogen -low enough not to interfere with the treatment-is given. GnRH agonists are effective for the relief of endometriosis-associated pain, but most patients experience genital spotting during the first month after the injection of GnRH agonist and it persists for a long time in some women and causes distress.

The purpose of this study was to evaluate the effect of MPA on genital spotting induced by GnRH agonist treatment.

MATERIALS AND METHODS

We analyzed 82 patients diagnosed with endometriosis by laparoscopic examinations who complained of genital spotting after GnRH agonist treatment at Chonnam National University Hospital. Those who did not complain of genital spotting after GnRH agonist treatment were excluded. All patients were administered same GnRH agonist, leuprolide acetate depot (Luphere depot 3.75 mg).

For the 82 patients who complained of genital spotting after the first injection of GnRH agonist, we supplied MPA at 10mg/day for seven days to 42 patients (group 1) and 14 days to 40 patients (group 2). We observed the discontinuation of genital spotting, the recurrence of genital spotting during the six months of GnRH agonist treatment, and compared the duration of days from the initiation of medication to the discontinuation of genital spotting, as well as the recurrence in the two groups.

The data were analyzed by SPSS version 21 and comparisons of the variables between groups 1 and 2 were performed using chi-squared tests with Yates' correction.

RESULTS

The median age of the patients in each group was 24 ± 6 (group 1) and 25 ± 5 (group 2) and there was no significant difference between the two groups (Table **1**). There were no significant differences in median body mass index and endometrial thickness checked by sonography between the two groups.

In both group 1 and 2, genital spotting stopped in all patients within 3-5 days after MPA administration (Table **2**). The duration from the initiation of medication to the discontinuation of genital spotting was not significantly different between the two groups. It showed that 10mg MPA for seven days was effective for the management of genital spotting occurring after the first injection of GnRH agonist. There was no further recurrence of genital spotting during the six months of GnRH agonist treatment period in either group.

Table 1: Patient Characteristics

	Group 1 (MPA 10mg/d for 7 days) (n=42)	Group 2 (MPA 10mg/d for 14 days) (n=40)	*p*-value
Age (years)	24 ± 6	25 ± 5	NS
BMI	21.4 ± 3.9	21.0 ± 2.6	NS
EM thickness (mm)	6.67 ± 2.8	7.16 ± 2.9	NS

Values are mean ± standard deviation, MPA, medroxy-progesterone acetate; BMI, body mass index; EM, endometrium; NS, nonspecific.

Table 2: Discontinuation of Genital Spotting and Recurrence after Medroxy-Progesterone Acetate Treatment

	Group 1 (MPA 10mg/d for 7 days) (n=42)	Group 2 (MPA 10mg/d for 14 days) (n=40)	*p*-value
Discontinuation of genital spotting	42 (100%)	40 (100%)	NS
Days from the initiation of MPA to the discontinuation of genital spotting	3.1 ± 2.0 days	3.4 ± 1.8 days	NS
Recurrence of genital spotting	0	0	NS

MPA, medroxy-progesterone acetate; NS, nonspecific.

DISCUSSION

Since Lemay and Quensel reported that GnRH agonist effectively lowered serum estradiol level compared to danazole in 1982 [9], GnRH agonists have been the primary medical treatment choice for endometriosis patients. GnRH agonists are derivatives of decapeptide GnRH. Natural GnRH is readily-accessible to proteases since it is not bound to circulating proteins and the half-life of GnRH in the circulation is only 3-6 minutes [10]. Analogs with D-amino acids in position 6 and with ethylamide substituted for the carboxy-terminal Gly^{10}-amide not only are more resistant to proteolysis but also have a higher affinity for the receptor. The affinity can be further increased by the introduction of bulky hydrophobic groups at the sixth amino acid position, which stabilizes the active configuration of the hormone analog and frequently increases protein binding in the circulation, thus increasing the half-life. GnRH agonists have initial stimulatory actions leading to gonadotropin release (flare effect) but after 7-14 days, it gradually inhibits the secretion of gonadotropins, thereby lowering serum estrogen levels. The biochemical mechanism of the agonist's action is unclear but the desensitization of gonadotropin receptors and loss of unoccupied receptors (downregulation) are thought to be involved.

The prolonged suppression of gonadotropins by GnRH agonists results in symptoms of estrogen deficiency, especially decreases in bone density, so the use of GnRH agonist is limited to no more than six months. However, in many studies, bone density did not change significantly at low estrogen levels (below 20pg/ml) and decreases in the bone density were shown to be reversible [11, 12].

The effects of GnRH agonists to decrease endometriosis lesions have been studied extensively [13, 14]. The results of GnRH agonist treatment for endometriosis-related pain, including pelvic pain, dysmenorrhea, and dyspareunia have been gratifying [15]. After the completion of treatment, pain recurred in a considerable number of patients but the degree of pain was much less than before treatment. However, the effect of GnRH agonist treatment on endometriosis patients with infertility is unclear. The fertility rate after GnRH agonist treatment is known to be between 30% (Nafarelin 400mg, intranasal) and 52% (Nafarelin 800mg, intranasal) [13]. Hughes *et al*. reported no increase in fertility rates after GnRH agonist treatment in infertile patients with minimal-to-mild endometriosis [16].

The complications of GnRH agonists are related to the hypo-estrogenic state it causes, which results in significant discomfort to patients by causing side effects, such as vaginal dryness, facial flushing, or headache. Due to the common hypo-estrogenic side effects of GnRH agonists, efforts have been made to mitigate this problem by adding estrogens and/or progestogens or tibolone to GnRH agonist therapy (add-back therapy).

Besides these common complications associated with hypo-estrogenism, genital spotting is another common complication that occurs during GnRH agonist treatment. Most of the bleeding stops eventually but bleeding persists longer in some patients. The purpose of this study was to compare the effect of MPA treatment on genital spotting according to the duration of MPA treatment. In both group A (MPA 10mg/day for 7 days) and group B (MPA 10mg/day for 14 days), genital spotting ceased within 3-5 days and no further recurrence of genital spotting occurred during the six-month period of GnRH treatment.

In conclusion, 10 mg/day MPA for seven days was effective for managing genital spotting after GnRH agonist treatment, without recurrence during the six-month treatment period.

CONFLICTS OF INTEREST

None declared

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