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Efficacy of Gonadotropin-Releasing Hormone Agonist and an Extended-Interval Dosing Regimen in the Treatment of Patients with Adenomyosis and Endometriosis

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Key Words
Adenomyosis · Endometriosis · Gonadotropin-releasing hormone agonist · Medication

Abstract
Aims: To determine the effects of gonadotropin-releasing hormone agonist (GnRH-a) and an extended-interval dosing regimen in the treatment of patients with adenomyosis and endometriosis. ***Methods:*** This was a prospective observational study in the setting of a hospital outpatient clinic. Seventy women suffering from adenomyosis and endometriosis were randomly divided into 2 groups: extended-interval dosing (experimental group) and conventional dosing (control group). ***Methods:*** Patients in the experimental group received a 4-dose regimen (triptorelin 3.75 mg by intramuscular injection every 6 weeks for a total of 4 doses). The patients in the control group received a conventional regimen (1 injection every 4 weeks for a total of 6 doses). The main outcome measures were relief and recurrence of dysmenorrhea and related climacteric symptoms, reduction of uterine volume, and serum levels of 17-β-oestradiol (E_2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). ***Results:*** The reliving rate of dysmenorrhea was 100% in patients treated with both the new regimen and the convention regimen after 6 months. The uterine volume was reduced 37.6% and 39.2%, respectively. And the levels of LH, FSH and E_2 were decreased significantly ($p < 0.001$). The E_2 levels were reduced to the postmenopausal level. The hormone profile of the experimental group was similar to that of the control group ($p > 0.05$). ***Conclusion:*** The use of the extended-interval dosing regimen of triptorelin depot in patients with adenomyosis or endometriosis results in a consistent hypo-oestrogenised state, which is similar to that achieved by the conventional regimen. The new regimen reduces the cost of treatment.

Introduction

Gonadotropin-releasing hormone agonist (GnRH-a) is commonly used in the treatment of adenomyosis and pelvic endometriosis as the primary medical therapy or as adjuvant therapy to surgical treatment. Administration of GnRH-a by depot every 4 weeks is a well-established regimen worldwide. However, it is reported [1–2] that after a single dose of triptorelin depot, the suppression of secretion of follicle-stimulating hormone (FSH) is maintained for 3–4 weeks afterwards. In addition, the level of luteinizing hormone (LH) starts to normalize in 8 weeks and the 17-β-oestradiol (E_2) level starts to normalize in weeks 7 and 8. These results suggest that the triptorelin depot can be given in an extended-interval

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Table 1. Clinical characteristics of patients

	Age, year	Parity	CA_{125} (KU/l)	r-AFS stage
Experimental group (n = 35)				
Adenomyosis (n = 20)	38.6 ± 2.8	1 (0–2)	102.8 ± 63.2	
Adenomyomata (n = 5)	31.3 ± 3.0	0	86.7 ± 45.9	
Endometriosis (n = 10)	32.3 ± 2.3	0 (0–1)	96.6 ± 40.2	I (n = 1), II (n = 5), III (n = 4)
Control group (n = 35)				
Adenomyosis (n = 20)	37.3 ± 3.2	1 (0–2)	98.8 ± 58.1	
Adenomyomata (n = 5)	29.6 ± 3.4	0	79.3 ± 43.5	
Endometriosis (n = 10)	31.3 ± 1.2	0 (0–1)	87.8 ± 38.6	II (n = 6), III (n = 3), IV (n = 1)

dosing regimen. The present study was thus designed to determine the effects of triptorelin in the treatment of patients with adenomyosis and endometriosis, using a 6-week triptorelin depot dosing regimen.

Materials and Methods

Patients

Forty women with newly diagnosed adenomyosis that required drug treatment were enrolled to this study. The clinical diagnosis of adenomyosis was based on the following criteria: (1) increasing dysmenorrhea; (2) firm enlarged uterus detected by pelvic examination and ultrasound examination or MRI in the myometrium; and (3) increasing serum CA_{125}. The study also included 30 women with an operative and pathologic diagnosis of adenomyomata (10 patients) or endometriotic ovarian cyst (20 patients) receiving post-operative adjuvant therapy with triptorelin. The severity of endometriosis was scored according to the revised American Fertility Society classification (1985). All patients, 19–40 years of age, with regular 26- to 32-day menstrual cycles, were recruited from January 2005 to June 2007, having different degrees of dysmenorrhoea, but no hormone use in the 6 months before the study. These patients were told to use barrier contraception during the treatment. 70 patients were randomly divided into 2 groups: extended-interval dosing (experimental group) and convention dosing (control group). There were 20 adenomyoses, 5 adenomyomata and 10 endometriotic ovarian cysts in the experimental group. There were no significant differences in severity of diseases and age between the two groups. The clinical characteristics of the patients are summarised in table 1.

Treatment and Clinical Observation

Patients in the experimental group were given 4 doses of triptorelin depot 3.75 mg by intramuscular injection (1 dose every 6 weeks), and the control group were given 6 doses of the same treatment (1 every 4 weeks). For all the patients, blood samples were taken to determine the serum hormonal profile of LH, FSH and E_2 before each injection and at the end of the treatment (week 24 of the study). The first blood sampling and administration of triptorelin were performed in the early follicular phase (between days 1 and 3 of the menstrual cycle). The clinical goal of the treatment was set to reduce the E_2 level to the postmenopausal level. All tissue samples were obtained with full and informed patient consent.

The degree of dysmenorrhoea scores during the study period was recorded by a chronic pain grade questionnaire [3, 4]. Using measures of pain intensity, activity limitations and disability, this questionnaire classifies respondents into 1 of 5 hierarchical pain grades: pain free (grade 1), low disability and low intensity (grade 2), low disability and high intensity (grade 3), high disability and moderately limiting (grade 4) and high disability and severely limiting (grade 5). Of 40 patients with adenomyosis, the size of the uterus was measured by ultrasound, and the uterine volume was calculated by the equation $0.523 \times a \times b \times c$, where a, b and c stand for uterine length, width and thickness, respectively.

Climacteric symptoms including hot flushes, sweats, vaginal dryness and other side effects from injection of triptorelin were observed. Patients were followed up every 3 months for 6 months from the end of treatment.

Data Analysis

The Wilcoxon signed rank sum test was used to assess the extent of reduction in hormone levels after triptorelin administration. The 2-sample t test was used to compare dysmenorrhoea score and uterine volume between the two groups. The 2-sample t test or the Fisher's exact test was applied to compare recurrence and no-recurrence groups of dysmenorrhoea on the basis of age, baseline serum CA_{125} and uterine volume, and history of operation. The threshold for statistical significance was set at $p < 0.05$. The Statistical Package for Social Science 13.0 was used for all statistical analyses.

Results

Clinical Outcome

The clinical outcome is shown in table 2. The dysmenorrhoea of all patients disappeared after triptorelin treatment. For the experimental group, the mean dysmenorrhoea score before treatment was 2.9 ± 1.1 and was decreased to 1.4 ± 1.5 during the follow-up visit 6 months after medication was completed, indicating a significant

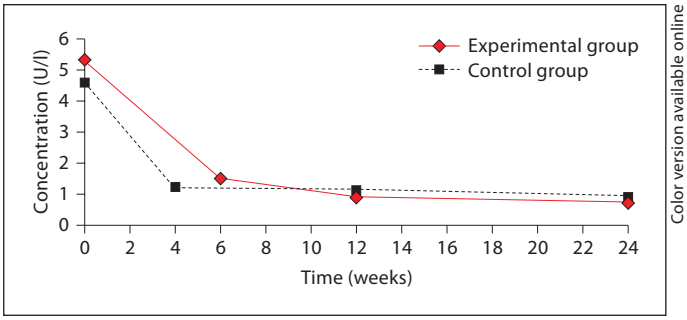

Fig. 1. Mean levels of LH during and after treatment with two regimens of triporelin.

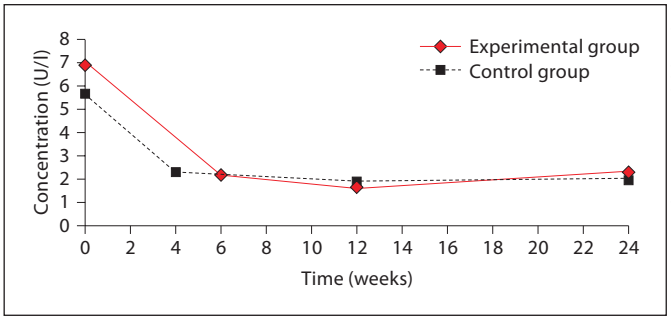

Fig. 2. Mean levels of FSH during and after treatment with two regimens of triporelin.

Table 2. Comparison of dysmenorrhoea and uterine volume before and after treatment for 2-regimen group

	Dysmenorrhoea (symptom score)			Uterine volume[c] (cm^3) (n = 40)		
	before treatment	after treatment[a]	p	before treatment	after treatment[b]	p
Experimental group	2.9 ± 1.1	1.4 ± 1.5	<0.05	240.0 ± 71.2	149.8 ± 36.3	<0.05
Control group	2.6 ± 1.0	1.1 ± 1.3	<0.05	238.0 ± 68.3	144.7 ± 33.5	<0.05
p	>0.05	>0.05		>0.05	>0.05	

[a] 6 months after medication. [b]At the end of the medication. [c] Size of uterus with adenomyosis.

therapeutic effect ($p < 0.05$). Similar changes in the score were observed with the control group: the mean score was decreased from 2.6 ± 1.0 (before treatment) to 1.1 ± 1.3 (after treatment) ($p < 0.05$), indicating that the two regimens were equally effective ($p > 0.05$ between the two groups).

The effects of the treatments as measured by the change of uterine volume were found to be equal in the two groups (table 2). In the patients with adenomyosis, the mean uterine volume decreased from a pretreatment volume of 240.0 ± 71.2 cm^3 to 149.8 ± 36.3 cm^3 at the end of the treatment in the experimental group (reduced by 37.6%), and from 238.0 ± 68.3 cm^3 to 144.7 ± 33.5 cm^3 in the control group (reduced by 39.2%), indicating that no differences in clinical efficacy were observed between the two groups.

Hormonal Profile

The serum LH level was reduced during the course of treatment with the extended-interval dosing regimen or the conventional regimen. It was decreased from a pretreatment level of 5.3 ± 2.1 U/l to 1.5 ± 1.1 U/l in week 6 in the experimental group, and the level was decreased from 4.6 ± 1.9 U/l to 1.2 ± 0.9 U/l in week 4 in the control group (fig. 1). The LH level remained low, until week 24 (6 weeks after the last dosing).The reduction of the LH level was statistically significant throughout the 24-week treatment period for each group ($p < 0.001$). However, there were no statistical differences in changes in the serum LH levels between the experimental group and the control group ($p > 0.05$).

The mean serum FSH was decreased from a pretreatment level of 6.9 ± 2.3 U/l to 2.2 ± 1.9 U/l in week 6 in the experimental group, and from 5.7 ± 2.1 U/l to 2.3 ± 2.0 U/l in week 4 in the control group (fig. 2). The differences of the serum FSH level in the different observational periods between pretreatment and after the therapy were statistically significant for each group ($p < 0.001$ for all comparisons). Nevertheless, the changes in the serum FSH levels were essentially the same in the two groups throughout the 24-week treatment period ($p > 0.05$).

The mean serum E_2 was decreased from a pretreatment level of 198.7 ± 27.3 and 189.8 ± 25.4 pmol/l to 95.0 ± 18.3 and 90.7 ± 16.2 pmol/l after the first injection in the experimental group and control group, respectively

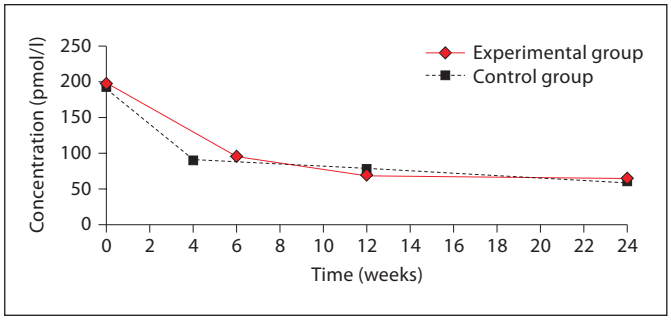

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Fig. 3. Mean levels of E_2 during and after treatment with two regimens of triporelin.

Table 3. Dysmenorrhoea recurrence for 2-regimen group

Characteristic	Recurrence	No recurrence	Rate of recurrence
Experimental group	11	24	31.4%
Adenomyosis (n = 20)	9	11	45.0%
Via operation[a] (n = 15)	2	13	13.3%
Control group	9	26	25.7%
Adenomyosis (n = 20)	7	13	35.0%
Via operation[a] (n = 15)	2	13	13.3%

[a] Including patients with adenomyomata and ovarian cyst.

(fig. 3). The concentration of E_2 continued to decrease throughout the study period, and the posttreatment level in the two groups reached postmenopausal levels up to 6 weeks after the last dose of triptorelin. The hormonal changes showed similar patterns for both LH and FSH.

Follow-Up Visit and Side Effects

All patients were followed up for 6 months after the end of the 24-week treatment period. The mean interval from the end of the treatment period to the resumption of menstruation was 77 days (range 60–112 days) in the experimental group and 82 days (range 65–120 days) in the control group. Some of the patients had dysmenorrhoea after the resumption of menstruation. The recurrence rates of dysmenorrhoea were 31.4% (11/35) in the experimental group and 25.7% (9/35) in the control group. The difference between the two groups was not statistically significant ($p = 0.792$; table 3). Of the 30 patients who received laparoscopy (resection of local adenomyomata or removal of endometriotic cyst), there were only 4 (13.3%) with recurring dysmenorrhoea after medication, but for those who did not receive the operation the rate was 40.0% (16/40; $p < 0.05$). Of the patients with adenomyosis, 9 in the experimental group and 6 in the control group had their uterine volume recovered to the size of pretreatment within 6 months after the end of treatment.

No patients had experienced climacteric symptoms such as hot flushes, sweats, and vaginal dryness by the mid-point of the treatment period (12 weeks). During the second half of the treatment period, the incidence rates of the side effects were 25% in the experimental group and 30% in the control group. Nevertheless, for both groups, these side effects were mild and well tolerated, and no patient withdrew from the study due to the side effects (data not shown).

Discussion

The rationale behind the treatment of endometriosis with GnRH analogues is to suppress gonadal function through binding to its receptor to achieve a prolonged hypo-oestrogenised state, which allows the regression or suppression of the endometriotic lesions. Besides hypothalamic-pituitary axis, GnRH receptor is also detected in extrapituitary tissues, including the human ovary, breast, endometrium and ectopic endometrium [5, 6]. Oestrogen dependence is a firmly established feature of adenomyosis and endometriosis. In the present study, GnRH-a therapy demonstrated efficacy in improving dysmenorrhoea with the two diseases, reducing the size of the uterus of 40 patients with adenomyosis, and decreasing serum hormone levels. The serum E_2 reached a very low level in week 4 after the first triptorelin treatment, remaining a consistent hypo-oestrogenised state for the rest of the period.

It is well known that GnRH-a can treat adenomyosis and endometriosis. However, because of its high expense, side effects and bone resorption, the patients' acceptability and compliance are much lower than expected. There is preliminary evidence that triptorelin depot injection can suppress the pituitary-gonadal axis for up to 8 weeks from the injection of the last dose [1, 2]. A study demonstrates that, after a single dose of administration, leuprolin and triptorelin depots (3.75 mg) induce satisfactory ovarian suppression up to 6 and 7 weeks, respectively, with significantly reduced levels of endogenous LH [7]. Another study by Matteo et al. [8] reports a similar result. Triptorelin has a longer duration

of action, allowing its administration at a longer interval in these patients. The present study with a regimen of 4 doses, once every 6 weeks, showed that the hormonal profile of LH, FSH and E_2 significantly reduced in week 4 after the first injection of triptorelin and throughout the 24-week treatment period. E_2 decreased to postmenopausal levels. The regimen with 6-week administration depot in the present study demonstrated the similar satisfactory ovarian suppression, relieving dysmenorrhoea, diminishing the size of uterus and reducing the recurrence rate of dysmenorrhoea after medication, compared to the control group (4-week regimen). The mean duration from the injection of the last dose to the resumption of menstruation was quite similar for both regimens. The resumption of menstruation took a mean of 77 days after the extended-interval dosing regimen, comparable to 82 days after the conventional regimen. A study from Italy reported a mean interval of 67–82 days after the last dose [2]. Therefore, the extended-interval dosing regimen may increase acceptability and patient compliance.

A few limitations of this study must be acknowledged. First, the use of the relative symptom score (chronic pain grade questionnaire) as a baseline before treatment might have led to a bias. It would be ideal to compare absolute symptom scores before and after treatment, but it is not easy for patients to define the absolute value of symptoms. We had to compare relative symptom scores because they are more intuitive. Second, the effects of the new regimen on fertility and bone loss have not been compared with the conventional regimen. Another limitation of this study was the relatively small sample size. Therefore, the results must be validated with a large-scale study.

In conclusion, the efficacy of an extended-interval (6-week) triptorelin dosing regimen is essentially the same as that of the conventional (4-week) regimen. The new regimen can reduce hormone levels to those needed for the treatment of adenomyosis and endometriosis for up to 24 weeks (6 weeks after the last injection), and also relieve dysmenorrhoea. Side effects are mild and tolerable. Moreover, the cost of the treatment can be reduced remarkably and therefore patient acceptance is increased.

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