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ORIGINAL ARTICLE

Effects of Three Month Treatment with Triptorelin on Pain Symptoms of Patients with Endometriosis

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ABSTRACT

Endometriosis is one of the most common gynecological diseases and pain , in the form of dyspareunia, chronic pelvic pain, and dysmenorrheal, is its most common feature. Gonadotropin-releasing hormone agonists have been studied in treatment of endometriosis patients. The aim of the present study is to evaluate the effect of Triptorelin (Variopeptyl 3.75mg) on pain symptoms among endometriosis patients.This study was a semi experimental interventional study. Twenty patients from Taleghani Hospital, Tehran, Iran, with symptoms of pelvic pain and endometriosis whose disease was confirmed by laparoscopy entered the study within a 6 months period. All patients received intramuscular injections of Triptorelin (Variopeptyl 3.75mg, Varian Darou Pajooh, Iran.) monthly for three months. VAS (visual analogue score) system was used to assess pain. Of 20 patients, who were enrolled in the study, 4 patients were excluded and 16 patients completed the study. The serum LH level decreased from a mean pretreatment level of 36.2 mIU/ml to 0.4 mIU/ml two weeks after completion of treatment. This reduction was statistically significant (p=0.004). Similarly E2 levels decreased from 701.6 pg/ml to 87 pg/ml which was statistically significant (p=0.037). All signs of pain were reduced after treatment compared to the pretreatment period. This reduction of pain was statistically significant.The use of Triptorelin for a three months period is effective in reducing endometriosis pain among patients.

Keywords: *Endometriosis, treatment, triptorelin, symptoms.*

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INTRODUCTION

Endometriosis is one of the most common gynecological diseases with a prevalence of about 10% of the general population [1]. The disease has several clinical presentations. Pain, in the form of dyspareunia, chronic pelvic pain, and dysmenorrhea is the most common feature causing patients to go to gynecological clinics [2]. Chronic pelvic pain is found in 70% to 90% of patients with endometriosis, but there is no relationship between disease severity and patients' symptoms [3]. Various methods are used to treat patients, including surgery, drug therapy or drug therapy after surgery. Hormonally active drugs act by blocking the ovarian function and producing a more stable hormonal environment. Oral contraceptives (OC), Danazol, progestogens, anti-progestogens and Gonadotropin-releasing hormone agonists (GnRH-a), have been used for treatment of endometriosis [4]. Contraceptive protection; long-term safety and control of menstrual cycle are their advantages. All these treatments act on the symptoms, decreasing them but not effectively treating the condition [5]. The evidence about the use of NSAIDs is inconclusive.

Clinicians are also recommended to use progestogens [medroxyprogesterone acetate (oral or depot), Dienogest, Cyproterone acetate, Norethisterone acetate or Danazol] or anti-progestogens (Gestrinone) as

one of the options to reduce endometriosis-associated pain. Gonadotropin-releasing hormone agonist treatments have been studied more than other medical treatments [3]. Treatment with these compounds is based on their ability to produce amenorrhea and anovulation [6].

Triptorelin is a synthetic analog of GnRH which is more potent than the native hormone and is more resistant to proteolysis. Triptorelin is marketed under the brand names Decapeptyl (IPSEN) and Diphereline and Gonapeptyl (Ferring Pharmaceuticals). In Iran Triptorelin is marketed under the brand name Variopeptyl (Varian Darou Pajooh, Iran).

There is a need for new medications, effective in the treatment of pain among endometriosis patients, with an acceptable side effect profile and suitable for long term use. The aim of the present study was to evaluate the effect of Variopeptyl 3.75mg on pain symptoms among endometriosis patients.

PATIENTS AND METHODS

This was a semi experimental interventional study, so treatment groups over time were its control. This study was approved by ethics committee and the institutional review board of Shahid Beheshti University of Medical Science.Twenty patients from Taleghani Hospital, Tehran, Iran, with symptoms of pelvic pain and endometriosis whose disease was confirmed by laparoscopy entered the study within a 6 months period. Patients with pelvic pain, dyspareunia, or dysmenorrhea were selected. Pain duration was at least 6 months. Symptoms among patients including: pelvic pain, dyspareunia, dysmenorrheal, and pelvic tenderness in the bimanual examination were examined before and after treatment. Study inclusion criteria were: age less than 45 years, no history of heart, lung and psychological diseases, and lack of medical treatment or surgery for endometriosis in the past two months.

Study design

Informed consent was obtained from all patients. The initial questionnaire was filled and patients were referred to a reference laboratory to check their luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) , and lipid profile such as triglyceride (TG), cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL). All patients received intramuscular injections of Triptorelin (Variopeptyl 3.75mg, Varian Darou Pajooh, Iran) monthly for three months. After completion of treatment the primary hormones and lipid profile were checked at the same laboratory. All samples were centrifuged and stored in -60 centigrade and all samples were taken after the completion of cases menstrual period. A second questionnaire was filled again at the end of the study.

VAS (visual analogue score) system was used to assess pain and pain and the pain was rated from zero to ten, from no pain to the worst pain ever perceived.

The questionnaire was prepared according to other studies and the experience of authors and was completed, corrected and validated by using the Delphi method with the help of experts, managers and professionals in the field.

To investigate the reliability of the questionnaire, especially regarding the signs and pain, 15 patients completed the questionnaire, and two weeks later the same patients completed the questionnaire again (without any medication) with a correlation coefficient of 0/86. Terms of reliability were tested in the laboratory tests, as well as tools and kits used.

Statistical analysis

Samples size was calculated with significant levels of 0/05 for a power of 80%, and a standard deviation of 0.5 in VAS readings. Paired sample t-test and Wilcoxon signed-rank test were used for analysis of the data and a p value less than 0.05 was considered significant. All statistical analyses were performed using SPSS version 21.0 (Armonk, NY: IBM Corp.).

RESULTS

Of 20 patients who were enrolled in the study, 4 patients were excluded from treatment and 16 patients completed the study. All patients were married, 15 patients (93.8%) with a history of infertility and 1patients (6.3%) without treatment. None of them had a history of surgery or medication for endometriosis before the study. The mean age of patients was 28.6 years and the mean body mass index (BMI) was 24.06.

Hormonal profile

The serum LH level decreased from a mean pretreatment level of 36.2 mIU/ml to 0.4 mIU/ml two weeks after completion of treatment. This difference was statistically significant (p=0.004). Similarly E2 level decreased from 701.6 pg/ml to 87 pg/ml which was also statistically significant (p=0.037), but FSH level changed from 8.9 mIU/ml to 6.6 mIU/ml which was not statistically significant (p=0.135) (Table 1).

Lipid profile

The mean of all laboratory findings for lipid profile (TG, CHOLESTROL, LDL, and HDL) did not show any statistically significant change (Table 1).

Clinical effects

All signs of pain after treatment were reduced compared to the pretreatment period. This reduction was statistically significant. The mean score of pelvic pain according to VAS was reduced from 4.5 to 2 (p=0.009), for dyspareunia it was reduced from 4.69 to 2.88 (p=0.005), for dysmenorrhea it was reduced from 5.81 to 4.44 (p=0.018) and for pelvic tenderness in bimanual examination it was reduced from 4.25 to 2.38 (p=0.016) (Table 1).

Side effects

After study completion patients filled a questionnaire regarding the symptoms caused by treatment which is summarized in table 2.

Table 1: Symptoms and laboratory findings among patients receiving treatment.

	t	df	Sig. (2-tailed)
pre_pelvic_pain - pos_pelvic_pain	2.988	15	.009
pre_dysparonia - pos_dysparonia	3.255	15	.005
pre_dysmenorrhea - pos_dysmenorrhea	2.668	15	.018
pre_pelvic_tenderness - pos_pelvic_tenderness	2.700	15	.016
pre_estradiol - pos_estradiol	2.285	15	.037
pre_FSH - pos_FSH	1.578	15	.135
pre_LH - pos_LH	3.374	15	.004
pre_TG - pos_TG	-.818	15	.426
pre_CHOL - pos_CHOL	-.757	15	.461
pre_HDL - pos_HDL	.247	15	.809
pre_LDL - pos_LDL	-1.247	15	.232

Table 2: Side effects of treatment reported by patients.

Symptoms	**Frequency**
Pruritus	**8/16**
Swelling	**12/16**
Hot flushes	**11/16**
Decreased libido	**14/16**
Depression	**8/16**
Frequency	**3/16**

DISCUSSION

The most common problems among patients with endometriosis are infertility and pain. Chronic pelvic pain causes distress as well as economic problems. The pain symptoms most commonly assigned to endometriosis are dysmenorrhea, dyspareunia, and chronic pelvic pain. Pain may be due to nociceptive, inflammatory, or neuropathic mechanisms, and there is evidence that all 3 of these mechanisms are relevant to endometriosis-associated pelvic pain [7]. Pharmacological agents for treatment of endometriosis are divided to first line treatments and second line treatments according to long term safety, symptoms control, efficacy, costs and availability. GnRH analogues are considered as second line of treatment in patients who have not responded to oral contraceptives or progestins or did not tolerate these drugs [6]. Gonadotropin-releasing hormone (GnRH) agonist therapy has been proven beneficial in the treatment of pain related to endometriosis. The addition of immediate add back therapy, appears to improve compliance and tolerability without sacrificing the therapeutic aim of pain relief.

The treatment for 3 months with a GnRH-a may reduce the painful symptoms for about 6 months [8]. We used the a three-months treatment period which in comparison with treatment duration of 6 months can control pain with fewer complications [9]. The interval for dosing regimen may be four weeks similar to our study, or six weeks [10]. With depletion of follicle- stimulating hormone, luteinizing hormone and estradiol we achieved the down regulation effect of GnRH agonists. This effect can induce amenorrhea, anovulation, and regression of endometriosis and reduces its associated clinical symptoms.

Standardized criteria and outcome measures used in clinical trials studying the pain in endometriosis would facilitate the comparison of different trials results [11]. Such standardized methods are visual

analog scale, McGill pain questionnaire, and quality of life scales such as SF-36 [12]. We used visual analog scale which indicated a significant reduction of pain symptoms after the completion of treatment.

The mechanism of action for the relief of pain is amenorrhea and progressive endometrial atrophy. The duration of pain relief differ according to the duration of treatment and the follow up period. For example in one study patients treated with a GnRH analogue for 6 months had a 53% rate of recurrence of symptoms 2 years after treatment [13]. We assessed the symptoms for only 2 weeks after the termination of treatment so our study was not suitable for evaluation of the duration of pain relief. It should be noted that there are differences in drugs action between GnRH analogues according to previous studies. For example in a study that used Triptorelin and Leuprorelin a gradual decrease of hormonal levels and lower rate of menopausal symptoms in leuprorelin group was observed [14]. Studies that have compared GnRH agonists with other components are numerous. In one study comparing these components and LNG-IUS, the GnRH-a group showed a significant decrease in the VAS and total endometriosis severity profile (TESP) score at the end of 1 year [15]. In a similar study Leuprolide and continuous oral contraceptives were equally effective in treatment of endometriosis-associated pelvic pain [16]. Another study showed that subcutaneous depot medroxyprogesterone acetate was statistically equivalent to Leuprolide in reducing four of five endometriosis symptoms or signs at the end of treatment (month 6), and in reducing all five symptoms after 12 months follow-up (month 18)[17].

These compounds have some side effects for example their effect on lipid profiles, but in our study no significant change was observed in lipid profiles as seen in a study by Al-Omari *et al.* [18]. In our study patients described some complications such as hot flushes, decreased libido, depression and frequency which were not significant. Some patients also complained of pruritus and swelling, in the injection site. The duration of treatment in our study was three months. If we prolong for the treatment to 6 months we might need to use Add back therapy to decrease the side effects.

Our study had some limitations such as relatively short follow up period and no evaluation of endometriotic lesions.

CONCLUSION

The use of Triptorelin for a three months period is effective in reducing endometriosis pain among patients.

CONFLICT OF INTEREST

None of the authors have any conflict of interest with the subject matter of the present study.

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