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Effects of simvastatin in prevention of pain recurrences after surgery for endometriosis

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Background: To compare efficacy of simvastatin with GnRHa (Decapeptyl 3.75 mg) on endometriosis-related pains following surgery for endometriosis.

Material/Methods: Sixty women with pelvic endometriosis, after laparoscopic diagnosis and conservative laparoscopic surgery, were treated with either simvastatin (n=30) for 16 weeks or Decapeptyl (n=30) every 4 weeks for 4 doses.

Results: Using VAS, the score of dyspareunia, dysmenorrhea, and pelvic pain 6 months after laparoscopic surgery declined significantly in both groups (p=0.001), but the difference between results of the 2 groups was not significant (p>0.05).

Conclusions: Both treatment modalities showed comparable effectiveness in the treatment of pains related to endometriosis.

Key words: statin • GnRHa • endometriosis • chronic pelvic pain • dysmenorrhea • dyspareunia

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Background

The presence of endometrial glandular and stromal cells outside the uterine cavity is called endometriosis. Endometriosis is one of the most common benign diseases affecting quality of life and fertility of women. Endometriosis is diagnosed by visual inspection of the pelvis during laparoscopy and positive histology confirms the diagnosis, but negative histology does not exclude it [1]. Multiple factors are responsible for endometriosis. The most important one is regurgitation of menstrual blood, but cytokines play a critical role in facilitation of the implantation of ectopic endometrial tissues [2]. Numerous data indicate that eutopic endometrial glandular and stromal cells may be functioning differently in women with endometriosis compared to normal endometrium in disease-free women [3]. Expression of Importin13, a possible marker for endometrial stem cells, compared to secretory endometrium, might support the hypothesis that this disease originates from stem cells [4]. The most prominent symptoms of endometriosis are dyspareunia, dysmenorrhea, pelvic pain, and infertility. All endometriosis lesion types are associated with pelvic pain and dysmenorrhea. Current treatment of endometriosis is mainly based on surgery and ovarian suppressive agents. Some medical treatments have been suggested for endometriosis, including oral contraceptive pills, medroxy progesterone acetate, and gonadotropin-releasing hormone agonists (GnRHa) [1]. In some studies statins were effective in prevention of endometriotic cells proliferation *in vitro*.

Statins are potent inhibitors of cholesterol biosynthesis to reduce serum cholesterol in patients with hyperlipidemia. Statins act by inhibiting 3-Hydroxy-3-Methyl Glutaryl Coenzyme A (HMG-CoA) reductase to block the conversion of HMG-CoA to L-mevalonate, a rate-limiting step in cholesterol synthesis. Statins were effective in inhibiting the mechanisms of cell proliferation and angiogenesis in experimental models for the development of endometriosis-like tissue [5–7]. In 1 study using a nude mouse model, simvastatin induced a dose-dependent decrease of the number and size of endometrial implants in mice. At the highest dose of simvastatin, the number of endometrial implants decreased by 87% and the volume by 98% [8]. In another study on endometriotic cyst walls and endometrial biopsy *in vitro*, atorvastatin treatment had no effect on $17\beta E_2$ levels in endometriotic stromal cell culture supernatant, and concluded that atorvastatin can be used as a treatment for endometriosis in humans [9].

Different studies have suggested that the role of statins in inhibition of aromatase activity may represent a new therapeutic option for endometriosis. After approval by ethics committee of Tehran University of Medical Sciences (TUMS) and after counseling with patients with pelvic endometriosis, we compared the clinical symptoms of patients after prescription of GnRHa with simvastatin.

Material and Methods

This study was conducted as a prospective, randomized, controlled trial to compare the effectiveness of simvastatin with that of GnRHa treatment, after surgery for endometriosis, on pain due to endometriosis. In our gynecology ward, all the patients with the laparoscopic diagnosis of pelvic endometriosis were included in the study. All of the subjects underwent conservative laparoscopic surgery. Laparoscopy was performed under general anesthesia, using the triple puncture technique. In laparoscopy, the surgeons tried to excise or ablate all the endometriotic implants and performed adhesiolysis. The night before laparoscopy, a data collection form was completed by a physician. The cause of laparoscopy and the severity of dyspareunia, dysmenorrhea, and pelvic pain were estimated by use of the Visual Analogue Scale test (VAS test), with a score of 0 being no pain and 10 being the most severe pain ever experienced. After the operation, the severity of endometriosis was entered into the data collection form as revised according to the American Society for Reproductive Medicine classification for endometriosis [1,10]. The staging was done intraoperatively by the 2 surgeons who were involved in the operations. Following ethics committee approval and obtaining informed consent in cases of simvastatin prescription, we prescribed simvastatin (film-coated tablet simvaHEXAL, 20 mg daily for 4 months) or GnRHa (Decapeptyl 3.75 mg IM each 28 day period for 4 doses) at the time of discharge. The patients were randomly assigned to either the simvastatin or Decapeptyl group (assigned to each group alternately in order of admission). Although the patient selection was random, in patients who wanted to become pregnant immediately, we had the obligation to prescribe simvastatin rather than GnRHa. None of the patients had a history of previous surgery or GnRHa treatment. We followed the patients for continuation of drugs and adverse effects of simvastatin. Each group had 30 patients and we tried to match the two groups for age, the severity of endometriosis and severity of endometriotic pain. Six months after operation, we reassessed the patients' symptoms by VAS.

We analyzed the data by SPSS 13, using the KS test (one-sample Kolmogorov-Smirnov test) for normality of data distribution, Levene's test for equality of variances, and independent samples t-test for equality of means for comparing quantitative normal data between the 2 groups, paired sample t-tests for comparing quantitative normal data between before and after treatment in each group and Pearson chi-square test for matching and comparing categorical variables between the 2 groups. According to the KS test, we compared the non-normal quantitative data by Mann-Whitney U nonparametric test between the 2 groups and Wilcoxon signed ranks test for comparing before and after treatment data in each group.

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Table 1. Comparison of marital status in two patient groups.

			Drug		Total
			Simvastatin	GNRH	
Marital status	Single	Count	12	13	25
		Percent	40.0%	43.3%	41.7%
	Married	Count	18	17	35
		Percent	60.0%	56.7%	58.3%
Endometrioma	No or <3cm	Count	12	5	17
		Percent	40.0%	16.7%	28.3%
	≥3 cm	Count	18	25	43
		Percent	60.0%	83.3%	71.7%
Total		Count	30	30	60
		Percent	100.0%	100.0%	100.0%

Results

In these 60 patients, 40 had endometrioma of ovary; the size of endometrioma was most often 3–10 centimeters (n=37). In this study, marital status of the 2 patient groups – the simvastatin group (S) and the GnRHa group (G) – was matched (P=0.793), but the difference for presence of endometrioma between the two groups was significant (P=0.045), (Table 1).

The major reasons for laparoscopy in the simvastatin group were infertility (40.0%) and ovarian cyst (33.3%) and ovarian cyst (40.0%) and dysmenorrhea (30.0%) in the GNRHa group (Table 2).

Severity of endometriosis in the 2 patient groups was not significantly different (P=0.253) (Table 3).

The severity of dyspareunia, dysmenorrhea, and pelvic pain before and after treatment were not significantly different between the 2 groups (Table 4). However, after treatment, the severity of dyspareunia, dysmenorrhea, and pelvic pain in the 2 groups was significantly reduced and the difference between before and after treatment in 3 parameters in each group was significant (Table 5). None of the patients showed adverse effects of simvastatin and all continued medical treatment for 4 months. Three of the patients in the simvastatin group became pregnant 4 months after surgery. All of them had mild endometriosis.

Discussion

The major finding of this prospective, randomized, double-blind trial of simvastatin *versus* Decapeptyl in the treatment of endometriotic pains was that after ablative surgery, prescription of simvastatin or Decapeptyl resulted in no significant difference in outcome.

Endometriosis is a common, often painful, condition, frequently associated with infertility. Endometriosis is found in 33% of infertile women [1]. Laparoscopy is recognized as the first option for diagnosis and treatment of endometriosis, but the rate of pain recurrence after conservative surgery is high. GnRH agonists have long been used successfully in the treatment of endometriosis [1,11–15], but because of their adverse effects (loss of bone minerals and vasomotor symptoms), physicians need better choices.

Statins, inhibitors of 3-hydroxy-3methylglutaryl-coenzyme A reductase (HMGCR), have been shown to decrease proliferation of several mesenchymal tissues. Actions of statins may be related to decrease in availability of cholesterol, as well as intermediate metabolites of mevalonate pathway downstream of HMGCR. Statin affects the growth of endometriotic tissues by inhibiting angiogenesis [8,16]. This could be important in non-hormonal and non-surgical treatment of endometriosis. The effectiveness of simvastatin in inhibition of endometriotic tissue has been confirmed *in vitro*. Proliferation of endometrial stromal cells has been inhibited with simvastatin in endometrial tissue obtained from 4 women with endometriosis. Therefore, it is suggested that simvastatin could potentially be a therapeutic agent for treatment of endometriosis [7]. The *in vitro* studies demonstrated that simvastatin induced a concentration-dependent inhibition of human endometrial stromal cell proliferation, evidenced by reduced DNA synthesis and a decrease in number of viable cells [7]. It has

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Table 2. Frequency of different reasons for laparoscopy in two groups.

Different reasons		Drug		Total
		Simvastatin	GNRH	
Infertility	Count	12	4	16
	Percent	40.0%	13.3%	26.7%
Dysmenorrhea	Count	3	9	12
	Percent	10.0%	30.0%	20.0%
Dyspareunia	Count	1	0	1
	Percent	3.3%	.0%	1.7%
Pelvic pain	Count	3	4	7
	Percent	10.0%	13.3%	11.7%
Ovarian cyst	Count	10	12	22
	Percent	33.3%	40.0%	36.7%
Infertility&ovarian cyst	Count	0	1	1
	Percent	.0%	3.3%	1.7%
Infertility&ovarian cyst& dysmenorrhea	Count	1	0	1
	Percent	3.3%	.0%	1.7%
Total	Count	30	30	60
	Percent	100.0%	100.0%	100.0%

Table 3. Severity of endometriosis in two patient groups.

Severity of endometriosis		Drug		Total
		Simvastatin	GNRH	
Minimal+mild	Count	13	9	22
	Percent	43.3%	30.0%	36.7%
Moderate	Count	10	8	18
	Percent	33.3%	26.7%	30.0%
Severe	Count	7	13	20
	Percent	23.3%	43.3%	33.3%
Total	Count	30	30	60
	Percent	100.0%	100.0%	100.0%

also shown that simvastatin inhibits the proliferation of stromal cells derived from human endometriotic implants in ovaries [5].

Simvastatin reduced both the number and volume of endometriotic lesions in nude mice in a dose-dependent manner. About 85% of the mice in the control group developed lesions, whereas 58% of the mice receiving low-dose simvastatin and only 17% of those given high-dose simvastatin had lesions. These findings suggested that the use of statins for treatment of endometriosis can be effective [8,17].

In our study, after conservative surgical treatment, the result of prescription of simvastatin (20 mg daily for 4 months) was similar to Decapeptyl (3.75 mg IM for 4 doses) in control of endometriotic pain.

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Table 4. comparison of age and severity of dyspareunia, dysmenorrhea and pelvic pain in two patient groups.

	Drug	N	Mean	Std. deviation	P value
Age	Simvastatin	30	28.83	5.814	0.614
	GNRH	30	29.77	5.643	
Dyspareunia before	Simvastatin	18	3.39	3.146	0.858
	GNRH	17	3.59	3.318	
Dysmenorrhea before	Simvastatin	30	6.00	2.613	0.185
	GNRH	30	6.63	3.211	
Pelvic pain before	Simvastatin	30	4.33	3.294	0.358
	GNRH	30	5.07	3.107	
Dyspareunia after	Simvastatin	18	1.06	1.349	0.386
	GNRH	17	1.59	1.661	
Dysmenorrhea after	Simvastatin	30	3.40	2.799	0.845
	GNRH	30	3.17	2.052	
Pelvic pain after	Simvastatin	30	1.97	2.042	0.083
	GNRH	30	2.83	2.001	
Dysmenorrhea(difference between before and after treatment)	Simvastatin	30	2.60	2.486	0.152
	GNRH	30	3.47	2.129	
Pelvic pain (difference between before and after treatment)	Simvastatin	30	2.37	2.773	0.882
	GNRH	30	2.23	1.654	
Dyspareunia (difference between before and after treatment)	Simvastatin	18	2.33	2.275	0.807
	GNRH	17	2.00	1.936	

Table 5. Comparison of parameters before and after treatment in each group.

		Mean	N	Std. deviation	P value
Simvastatin	Dyspareunia before	3.39	18	3.146	<0.001
	Dyspareunia after	1.06	18	1.349	
	Dysmenorrhea before	6.00	30	2.613	<0.001
	Dysmenorrhea after	3.40	30	2.799	
	Pelvic pain before	4.33	30	3.294	<0.001
	Pelvic pain after	1.97	30	2.042	
GNRH	Dyspareunia before	3.59	17	3.318	0.001
	Dyspareunia after	1.59	17	1.661	
	Dysmenorrhea before	6.63	30	3.211	<0.001
	Dysmenorrhea after	3.17	30	2.052	
	Pelvic pain before	5.07	30	3.107	<0.001
	Pelvic pain after	2.83	30	2.001	

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Limitations of study

Our study has some limitations. The sample size was small and the study must be repeated with larger sample sizes and with other doses of simvastatin. In addition, none of the patients accepted second-look laparoscopy to evaluate size and number of endometriotic lesions after medical treatment. Finally, our study lacked a third group without medical treatment after conservative surgical treatment.

The important aspect of this study is that it is the first to evaluate use of simvastatin to relieve endometriotic pains.

Further investigations without the limitations of the present study should provide more precise assessment of the effects of simvastatin on endometriotic lesions.

Conclusions

GnRHa is one of the most accepted medical treatments of endometriosis, but the role of statins in endometriosis had been assessed only *in vitro* or in animal models. Our study assessed the effect of simvastatin on symptoms of endometriosis and found that it is comparable with Decapeptyl.

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