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Original Article

Clinical efficacy and safety of gonadotropin-releasing hormone agonist combined with laparoscopic surgery in the treatment of endometriosis

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Abstract: Objective: Our aim was to investigate the clinical efficacy and safety of gonadotropin-releasing hormone agonist (GnRH-a) following laparoscopic surgery in the treatment of endometriosis. Methods: A total of 100 patients with endometriosis were randomly divided into a control group (laparoscopic resection only, n=50) and treatment group (laparoscopic resection combined with GnRH-a treatment, n=50). In addition to laparoscopic resection that was performed in the control group, the treatment group also received an additional 3-6 courses of GnRH-a therapy postoperatively (3.75 mg per time, every 28 days). The effective rates, recurrence rates, dysmenorrhea relief rates, dyspareunia relief rates, chronic pelvic pain relief rates, and the total pain relief rates as well as the adverse events were recorded and analyzed. Results: Total effective rates of the treatment and control groups were 86.0% (43/50) and 62.0% (31/50), respectively, with significant inter-group difference (P<0.05). Remission rates of the treatment and control groups were 54.0% (27/50) and 24.0% (12/50), respectively, with significant inter-group difference (P<0.05). The comparison of dysmenorrhea relief rates, dyspareunia relief rates, and chronic pelvic pain relief rates between treatment group and control group were all with significant differences (all P<0.05). Incidences of uterine bleeding, depression, acne, and weight gain were significantly lower in the treatment group compared with those of the control group (all P<0.05), whereas the incidence of genital dryness was significantly higher in the treatment compared with that of the control group (P<0.05). There were no differences regarding the incidences of hot flush, sleep disorder, and headache between the two groups (all P>0.05). Conclusion: Compared with laparoscopy use only, applying GnRH-a after laparoscopy can enhance treatment efficacy, increase pain relief rates, and reduce recurrence rates and partly adverse events.

Keywords: Laparoscopy, gonadotropin-releasing hormone agonist, endometriosis

Introduction

Endometriosis (EMS) is a benign disease with malignant biological behaviors including planting, metastasis, and recurrence for which surgical treatment and pharmacological treatment are the two main therapeutic strategies. In recent years, laparoscopic surgery has demonstrated great superiority in the treatment of EMS. The laparoscope enters the retroperitoneal space and identifies lesions with the magnifying effect, so as to significantly alleviate patient pain by surgical resection of ectopic lesions, separation of adhesions, and restoration of the normal anatomy within the pelvic cavity under clear vision. However, laparotomy is inevitably associated with postoperative incision pain, slow recovery, and prolonged hospital stay. According to the literature, even performed by experienced surgeons, the incidence of postoperative complications can reach 10% [1]. Moreover, since EMS lesions are characterized by deep and wide distribution, with surgery alone it is difficult to achieve satisfactory results as the postoperative annual recurrence rate is reportedly as high as 30% to 40% [2, 3]. Therefore, effective adjuvant therapy to prevent or delay the recurrence is urgently needed.

The primary purposes of pharmacological treatment of EMS are to relieve pain, reduce the lesions, and prevent recurrence. The commonly

used drugs include oral contraceptives, progesterone, Danazol, and so forth [4]. In the last few years, gonadotropin-releasing hormone agonist (GnRH-a) has become increasing popular in EMS treatment [5]. Long-term use of GnRH-a can reduce secretion of pituitary gonadotropin to decrease ovarian hormone levels, thereby causing temporary amenorrhea to achieve EMS recurrence prevention.

This prospective randomized controlled study aimed to investigate the clinical efficacy and safety of GnRH-a combined with laparoscopic surgery in the treatment of EMS and to provide a theoretical basis of combination treatment of EMS.

Materials and methods

Patients

The Medical Ethics Committee of Wuhan Children's Hospital reviewed and approved the protocol of this study and all patients provided the signed consent forms.

A total of 100 patients with EMS in the Department of Gynecology of Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science & Technology, China, scheduled for laparoscopic surgery from January 2011 to December 2014 were recruited into the study and randomly divided into a treatment group (n=50) and control group (n=50) using the random number table method. Patients in the treatment group received additional GnRH-a treatment after laparoscopic surgery, while those in the control group underwent laparoscopic surgery alone.

Inclusion criteria: women with EMS confirmed by histology; women not planning to conceive immediately; women with no contraindications against laparoscopy and GnRH-a.

Exclusion criteria: women that had hormone therapy 3 months prior to surgery; women with endocrine, immune, metabolic diseases, or malignant tumors; women that had laparoscopy or GnRH-a previously; women that had contraindications against either laparoscopy or GnRH-a.

Intervention

All of the recruited patients underwent standard laparoscopic surgical procedures including release of pelvic adhesions, resection of ovarian EMS, and ectopic lesion resection/electrocautery. In brief, after general anesthesia and routine disinfection, in the upper edge of the umbilical, a 1 cm incision was made for the pneumoperitoneum (CO_2, with pressure of 13 mmHg) needle puncture (Trocar). Laparoscopy was then positioned in the left and right lower abdominal cavity. The release of adhesion, removal of ovarian endometriotic cysts, and resection of EMS lesions were performed.

Patients in the treatment group received additional GnRH-a treatment. They were given a subcutaneous injection of GnRH-a with a dose of 3.75 mg on the first day after operation and continuously administered every 28 days, 4 to 6 times in total.

Follow up and outcome measures

All patients were regularly examined 1, 3, 6, and 12 months after operation to evaluate efficacy and complications. The outcome measures included complications, pain, gynecological examination results, adjuvant examination results, and clinical efficacy (remission rate, improvement rate, total effective rate, ineffective rate, and recurrence rate).

Pre- and post-operative pain evaluations

Pain scores were recorded before and one year after the operation. Cases that showed dysmenorrhea, sexual intercourse pain, and chronic pelvic pain were recorded during the follow up. The degrees of pain were evaluated using the number of digital scores (NRS) [6].

Clinical efficacy determination

Remission: the original pain symptoms were significantly reduced, meanwhile, the gynecological examination and vaginal ultrasound did not detect any pelvic mass; Improvement: the original degree of pain was reduced without any positive sign and no pelvic mass was detected in the physical examination; Ineffectiveness: the original pain symptoms did not improve with no obvious pelvic mass; Recurrence: 6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination.

Postoperative complications

Postoperative complications including uterine bleeding, depression, acne, weight gain, genital

Table 1. Baseline characteristics

	Treatment (n=50)	Control (n=50)	T or X^2	P
Age (years)	36.41±5.19	36.81±6.92	0.327	0.744
BMI (kg/m^2)	20.45±3.20	20.51±3.15	0.095	0.925
Age at menarche (yr)	14.50±1.20	14.60±1.50	0.368	0.714
Menstrual cycle			0.088	0.766
Regular	43 (86.0%)	44 (88.0%)		
Irregular	7 (14.0%)	6 (12.0%)		
Menstrual duration (days)	6.15±1.10	6.50±1.65	1.248	0.215
Menstrual amount			1.103	0.576
Small	5 (10.0%)	6 (12.0%)		
Moderate	34 (68.0%)	29 (58.0%)		
Large	11 (22.0%)	15 (30.0%)		
Size of endometrioma (cm)	5.15±1.90	4.60±1.45	1.627	0.107
Laterality of endometrioma			0.657	0.418
Unilateral	27 (54.0%)	31 (62.0%)		
Bilateral	23 (46.0%)	19 (38.0%)		
ASRM stage			2.291	0.130
β	38 (76.0%)	31 (62.0%)		
x	12 (24.0%)	19 (38.0%)		

Note: BMI: body mass index; ASRM: American Society for Reproductive Medicine.

Table 2. Evaluation of pain before operation

Group	Case	Dysmenorrhea	Chronic pelvic pain	Sexual intercourse pain
Treatment	50	5.35±3.00	5.35±3.00	5.35±3.00
Control	50	5.35±3.00	5.35±3.00	5.35±3.00
t		1.456	1.467	1.856
P		0.157	0.178	0.075

Table 3. Evaluation of pain after operation

Group	Case	Dysmenorrhea	Chronic pelvic pain	Sexual intercourse pain
Treatment	50	1.45±2.05	0.35±0.90	0.13±0.41
Control	50	1.55±2.73	0.64±0.15	0.64±1.03
t		0.207	2.247	3.253
P		0.836	0.027	0.002

dryness, hot flush, sleep disorder, and headache were documented and analyzed.

Statistical analysis

IBM SPSS 17.0 statistical software was applied for data analysis. Continuous data are expressed as mean ± standard deviation (mean ± SD) and inter-group difference was analyzed with independent t-test. Categorical data are expressed as percentages and compared using Chi-square test. All tests were performed using a two-sided test of significance and the significance level was 0.05.

Results

Baseline characteristics

Our present study enrolled a total of 100 patients from January 2011 to December 2014. The average age of the patients was 36.62±6.15 years. There were no significant differences in age, body mass index (BMI), age at menarche, menstrual cycle regularity, menstrual duration, menstrual amount, size of endometrioma, laterality of endometrioma, and ASRM stage between the two groups (all P>0.05, **Table 1**).

Pain evaluation

There were no significant differences in NRS scores regarding all three indices before operation and dysmenorrhea after operation between the two groups (all P>0.05, **Tables 2**, **3**). However, the NRS scores of sexual intercourse pain and chronic pelvic pain were significantly lower in the treatment group than those in the control group (both P< 0.05, **Table 3**). Also, relief rates of dysmenorrhea and chronic pelvic pain were significantly higher in the treatment group than those in the control group (all P<0.05, **Table 4**).

Clinical efficacy

There were 27 patients with remission and 16 with improvement in the treatment group, indicating an obviously higher total effective rate (86.0%, 43/50) compared with the control group (62.0%, 31/50, P<0.05). The difference of the ineffective rate between the two the groups was not statistically significant (P>0.05). The recurrence rate of the treatment group was

Table 4. Pain relief rates after operation

Group	Case	Dysmenorrhea	Chronic pelvic pain	Sexual intercourse pain
Treatment	50	11/13 (84.6%)	18/20 (90.0%)	4/7 (57.1%)
Control	50	4/11 (36.4%)	13/22 (63.6%)	1/2 (50.0%)
χ^2		5.919	5.177	0.032
P		0.015	0.023	1.000

Table 5. Comparison of clinical efficacy between the two groups

Group	Treatment	Control	χ^2	P
Case	50	50		
Remission	27 (54.0%)	12 (24.0%)	9.458	0.002
Improvement	16 (32.0%)	19 (38.0%)	0.396	0.529
Ineffective	1 (2.0%)	4 (8.0%)	0.454	0.677
Recurrence	6 (12.0%)	15 (30.0%)	4.882	0.027
Total effective	43 (86.0%)	31 (62.0%)	7.484	0.006

Table 6. Comparison of adverse events between the two groups

	Treatment (n=50)	Control (n=50)	χ^2	P
Uterine bleeding				
Menstruation-like bleeding	1 (2.0%)	27 (54.0%)	33.532	<0.001
Spotting	11 (22.0%)	28 (56.0%)	12.148	<0.001
Irregular bleeding	0	6 (12.0%)	4.433	0.035
Hot flush	6 (12.0%)	5 (10.0%)	0.102	0.645
Genital dryness	8 (16.0%)	2 (4.0%)	4.000	0.046
Depression	2 (4.0%)	8 (16.0%)	4.000	0.046
Sleep disorder	4 (8.0%)	6 (12.0%)	0.444	0.505
Acne	2 (4.0%)	10 (20.0%)	6.061	0.014
Headache	2 (4.0%)	3 (6.0%)	0.000	1.000
Weight gain	0	7 (14.0%)	5.530	0.019

significantly lower than that of the treatment group (P<0.05). The difference of recurrence rate between the two groups was unremarkable (P>0.05, **Table 5**).

Adverse events

In this study, none of the patients had adjacent organ damage and they were discharged 2 to 6 days after surgery. Incidences of uterine bleeding, depression, acne, and weight gain were significantly lower in the treatment group than those in the control group (all P<0.05) while the incidence of genital dryness was significantly higher in the treatment than that in the control group (P<0.05). In addition, there were no differences regarding the incidence of hot flush, sleep disorder, and headache between the two groups (all P>0.05, **Table 6**).

Discussion

In this study, we compared the therapy of GnRH-a combined with laparoscopic surgery and laparoscopic surgery alone for the treatment of EMS. The results demonstrate that combination therapy was more effective and safe.

Recently, surgery has become the mainstay method in EMS treatment [7]. However, as EMS is characterized by severe pelvic adhesions and deep lesions, lesions are extremely difficult to completely clean, thus, leading to high recurrence rate [8]. Therefore, an effective postoperative adjuvant therapy for the prevention of recurrence is necessary.

Laparoscopy is another commonly used method for diagnosis and treatment of EMS. However, laparoscopy shows limitations in diagnosis and treatment of extraperitoneal lesions, especially in the determination of the depth and extent of the lesions [9]. Hence, it is unsuitable for patients with severe pelvic adhesions to receive laparoscopic surgery which may damage adjacent organs. However, with magnifying effect, laparoscopy provides clear vision which makes it easier to have access to the retroperitoneal area [10]. The findings in our present study prove that laparoscopy can significantly alleviate pain including dysmenorrhea, chronic pelvic pain, and sexual intercourse pain. Additionally, there were no severe complications observed. All patients recovered rapidly and were discharged from the hospital 2-6 days after surgery.

In recent years, clinical application of GnRH-a has gradually increased [11-13]. GnRH-a, a 10-peptide neurohormone secreted by the hypothalamus, is closely related to the nervous, immune, and endocrine systems and can regu-

late reproductive functions [14]. The effectiveness of GnRH-a in the treatment of EMS has been well recognized as it can decrease secretion of gonadotropin in pituitary by inhibiting hypothalamus-pituitary-ovarian axis (HPO axis), so as to decrease ovarian sex hormone levels and cause degradation of hormone-dependent ectopic endometrium, therefore resulting in atrophy of ectopic endometrium [15]. The previous study demonstrated that the use of GnRH-a only for 6 months could effectively relieve pain and reduce the size of the EMS lesion. However, symptoms quickly relapsed and the lesions returned to the original sizes 6 months after the withdrawal of medication [16]. Postoperative GnRH-a could cause a series of side effects including osteoporosis, hot flashes, sweating, vaginal dryness, and loss of libido which can be treated with add-back therapy of an estrogen supplement.

According to previous reports, the recurrence rate of EMS was approximately 13-34%, mainly due to the difficulties of surgery caused by severe adhesions and infiltrations of lesions [17]. For safety considerations, it is inevitable to leave some residual lesions which can easily relapse under the influence of estrogen. In addition, some patients choose to have conservative surgery with the desire to maintain their reproductive functions [18, 19]. Therefore, postoperative adjuvant drug therapy is critical for inhibition of residual lesion proliferation and prevention of recurrence. In the present study, we treated ectopic endometrium which is difficult to detect or remove with surgery, by using GnRH-a to inhibit the HPO axis, so as to further relieve patient pain and prevent or delay recurrence. Compared with those of the control group, the relief rates of dysmenorrhea (84.6%) and chronic pelvic pain (90.0%) in the treatment group were significantly higher (both $P<0.05$) and the remission and total effective rates in the treatment group were significantly higher than those of the control group (both $P<0.05$). These findings were consistent with the reports of Li et al. [20].

Our study also has some limitations. First, the sample size was limited, therefore, a larger sample size will be needed for further study and to fully evaluate the clinical efficacy and safety of this combination treatment. Second, the follow up duration was only one year. A longer follow up time will be necessary to further evaluate long-term clinical outcomes.

In conclusion, even though laparoscopic conservative treatment of EMS is reliable, the recurrence rate is still high. However, GnRH-a combined with laparoscopic surgery is more effective and can reduce or delay recurrence.

Disclosure of conflict of interest

None.

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