

Efficacy Analysis of an Experience on Development of the Combination Therapy Protocol for Endometriosis Management

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Abstract

Purpose: Endometriosis can be managed effectively by medication, surgery, or a combination of both. Numerous studies have been conducted on surgical and medication treatment options, but their results are still under discussion. Therefore, we performed a study to develop a combinational treatment for various stages of endometriosis. **Methods:** Over a 3-year period, 218 documented endometriosis patients were classified in 4 stages. After first laparoscopy (with electrocoagulation and adhesion removal for stages I to III), the patients were treated with GnRH analogs (Gonadotropin Releasing Hormone Agonist-375 mg of Decapeptyl) for 3, 6 & 6 months, respectively. The second and third laparoscopy procedures were performed after 3 and 6 months, with add-back therapy. The treatment was evaluated by direct observation based on laparoscopic view and the pain relief was measured by the VAS (Visual Analogue Scale) after the first step of medication for patients of stages I-III. **Results:** After 3 months, 70/76 patients (91.9%) with stage-I endometriosis showed complete recovery (six cases after 6 months) while 65/72 and 32/43 cases with stage-II and -III (90.3 and 74.4%), respectively, showed complete recovery after 6 months of treatment. The remaining patients had GnRH treatment for another 3 months, and all showed a complete recovery after 9 months. Furthermore, 12 of the patients with stage-IV symptoms were candidates for laparoscopy or laparotomy, and their treatment response rate was 55.6%. The pain relief was significant after the combinational treatment in patients with stages I-III ($P = 0.0001$). **Conclusion:** Our study showed efficacy of the developed protocol for the endometriosis management.

Keywords

Endometriosis, Combinational Therapy, Management, Protocol Development, Efficacy

1. Introduction

The presence of stromal endometrial glands outside the uterus is the classic definition of endometriosis. Endometriosis is a chronic gynecological disorder that commonly manifests as dysmenorrhea, chronic pelvic pain, and infertility. It is one of the most prevalent diseases in women of reproductive age worldwide, as well as the third leading cause of hospitalization in women [1] [2] and one of the main reasons for hysterectomies [3]. The exact prevalence of endometriosis is not known, but its estimated and reported range in previous studies is from 2% to 10% in women of reproductive age [4] [5], 38% to 50% in infertile women [6] [7], and up to 87% in women with chronic pelvic pain [7]. Therefore, it appears that the effective treatment of this disabling condition is necessary and should be a priority before the initiation of assisted reproductive treatment for infertile and subfertile women [8].

Endometriosis may be managed with medication, surgical treatment, or the combination of both strategies. Previous studies have been conducted on surgical and medication-based treatments, but these strategies require additional development to enhance their efficacy [9] [10]. Laparoscopy is accepted as the diagnostic gold standard and one of the main treatment methods for endometriosis [11] [12] [13] [14]. While medications could be effective following the removal of endometrial lesions [15] [16], no explanation exists for the ineffectiveness of medication treatment before endometriosis cysts or spots are removed [16] [17] [18] [19]. The need for drug treatment after laparoscopy has also been indicated by previous studies [20] [21] [22], and the use of 6-month gonadotropin-releasing hormone (GnRH) agonist therapy following laparoscopy prevented endometriosis recurrence [23]. Presently, new endometriosis treatment strategies are required and should be developed. Therefore, we conducted a study to develop a combinational treatment approach by determining the appropriate intervals for treatment assessment and surveying the efficiency of this approach. Specifically, we used direct observation with laparoscopy at various stages of documented endometriosis and assessed the pain relief provided to female patients of reproductive age.

2. Material & Methods

This was a non-experimental interventional study conducted with 218 patient volunteers from Sarem Women's Hospital Endometriosis Clinic from April 2013 to January 2016. The patients had documented endometriosis and were unresponsive to oral contraceptive pill (OCP). Patients with colorectal or bladder invasion of endometriosis or both were excluded from the study. The Hospital Ethical Committee approved the study with approval letter No. 8909-877. The patients were completely informed about the treatment procedures and provided an informed signed consent form. Then, the patients commenced the study and were treated using our designed treatment protocol, which was followed by a second and third observational laparoscopy for advanced stages of endometriosis. The treatment protocol was successfully piloted in 2012 with 47 patients and has been improved in this study using a greater sample size.

In the first laparoscopic procedure, the endometriosis was diagnosed, and the stage was defined based on the revised American Society for Reproductive Medicine (ASRM) classification of endometriosis [24]. Based on this procedure, the patients were classi-

fied into four stages (I-IV) of endometriosis with the supervision and observation of the Chief Surgeon.

Our treatment protocol design included the use of a GnRH agonist to loosen the endometriosis lesions; then, we allowed the appropriate period to elapse (3-month interval). Then, we evaluated the condition by direct observation to determine the requirement for further minimal invasive surgical procedures such as electrocoagulation, dissections, adhesion removal, and cyst excision (this recent option performed only for endometrioma cysts) based on the existing guidelines and recommendations [25]-[30]. The endometrioma cysts were also confirmed based on tissue diagnosis. It is noteworthy that in the first laparoscopy, the surgical intervention was performed for all the patients except those in stage-IV. No surgical intervention was performed in stage-IV because this was postponed until after the second observation following the 9-month GnRH agonist treatment. The 375 mg dose of decapeptyl (triptorelin) as the GnRH analog was injected monthly, and the first medication duration was set as follows based on our previous experience in the pilot study:

- 3 months for stage-I.
- 6 months for stage-II and III.
- 9 months for stage-IV.

The medication duration was 3 months longer in each subsequent stage when necessary based on the additional laparoscopy. The thirdobservational laparoscopy procedures were needed for stage-III and -IV patients. The add-back therapy (OCP) was initiated for patients who were candidates for a longer than 6-month GnRH agonist therapy [31]. The study scheme of the surgical-medical protocol development for this endometriosis treatment is illustrated in **Figure 1**. As it mentioned before, the treatment was evaluated by patients' symptoms and the direct observation based on

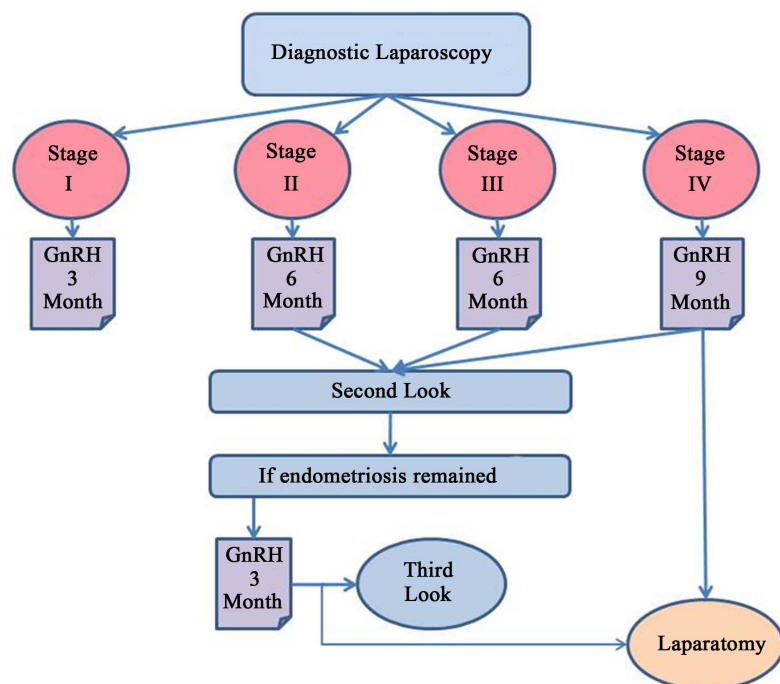


Figure 1. The study management protocol.

laparoscopic view as the chief surgeon rate the condition based on ASRM checklist for classification of endometriosis. So, any changes involving the reduction, curing or increasing of the endometriosis were recorded. For patients with ethical limitation for further laparoscopic procedure (like the stage-I patients for second look laparoscopy), only clinical symptoms were the criteria for the patient curing. Accordingly, the pain relief was measured by the VAS (Visual Analogue Scale) after the first step of medication and before the last laparoscopy for patients of stages I-III (In Stage-I after 3 months, Stage-II & -III after 6 months patients rate their pain from 1 to 10). The VAS is a simple tool like a ruler for visualizing and quantifying of the pain severity that perform by the patients themselves.

The data were analyzed by SPSS software V.23 using descriptive statistics and paired t-test as the analytical statistical test.

3. Results

In this study among the 218 patients, 76, 72, 43, and 27 (34.9%, 33%, 19.7%, and 12.4%) were in stage-I, -II, -II, and -IV, respectively. The mean age and body mass index (BMI) of the patients was 31.11 ± 4.69 years and 24.30 ± 3.79 , respectively. These data and the symptom frequencies are shown in **Table 1**.

The results of the endometriosis management revealed that 83.5% of all patients and 87.43% of those with stage I-III were cured by the first step of the therapeutic method, which increased to 93.6% of all patients after the initiation of the second step of the protocol. The protocol was beneficial in relieving the pain of 77.52% of patients. Pain relief significantly decreases after the initial treatment step of the protocol ($P = 0.0001$, **Figure 2**). Interestingly, the visceral endometriosis symptoms were cured following the drug therapy phase of the protocol. As it show in **Table 2**, at the stage-I of endometriosis 91.9% of the patients were cured after 3 months GnRH agonist treatment (data was based on their clinical symptoms) and 90.3% of Stage-II patients were cured after 6 months medication after initial laparoscopy. Continuing the medication for further 3 months relief the symptoms for all of the remained patients with stage-I & -II of endometriosis. Initial laparoscopy with 6 months medication is curable for 74.4% of the

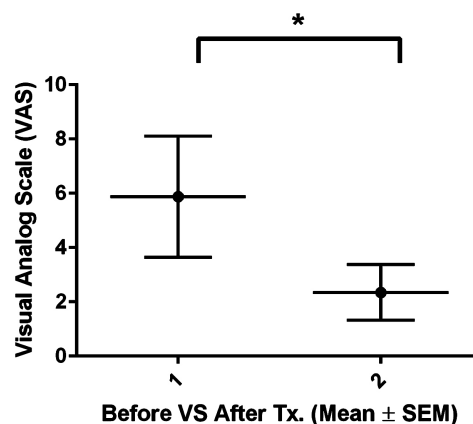


Figure 2. Pain relief assessment using visual analogue scale (VAS) for patients with endometriosis after initial combinational treatment protocol. *Paired T-test; $t = 21.354$, $df = 217$, P -value: 0.0001.

Table 1. Distribution of patients by endometriosis stage, age, body mass index (BMI), and symptoms.

Endometriosis stage	Frequency (%)	Age mean \pm SD	BMI mean \pm SD	Symptoms/presentations	
				Dysmenorrhea	Pelvic pain
Stage I	76 (34.9)	30.88 \pm 4.39	25.13 \pm 3.66	57 (26.15)	13 (5.96)
Stage II	72 (33.0)	30.70 \pm 4.96	24.43 \pm 3.78	56 (25.69)	9 (4.13)
Stage II	43 (19.7)	31.07 \pm 4.82	22.56 \pm 3.52	29 (13.3)	6 (2.75)
Stage IV	27 (12.4)	32.96 \pm 4.31	24.27 \pm 3.96	22 (10.09)	9 (4.13)
Total	218 (100)	31.11 \pm 4.69	24.30 \pm 3.79	164 (75.23)	37 (16.97)

Table 2. Outcome of patients with endometriosis after combinational treatment protocol.

Endomet-riosis stage	Frequency	Initial procedures	Cured persons with initial procedures	Cured persons after more GnRH Tx.	Laparoscopy		Symptoms reduction/pain relief after Initial procedures	Cure based on:	Relapse after 1 year
					Second observation	Third observation			
Stage I	76	Lap. Tx + GnRH for 3 months	70 (91.9%)	6 (8.1%) (6 persons cure after another 3-months GnRH)	0	0	70 (91.9%)	Only patients with pain relief	8 (10.5%)
Stage II	72	Lap. Tx + GnRH for 6 months	65 (90.3%)	7 (9.7%) (7 persons cure after another 3-months GnRH)	7	0	61 (84.72%)	Lap. direct observation followed by pain relief	16 (22.2%)
Stage II	43	Lap. Tx + GnRH for 6 months	32 (74.4%)	11 (25.6%) (9 persons cure after another 3-month GnRH treatment)	11	2	28 (65.11%)	Lap. direct observation	10 (23.3%)
Stage IV	27	Dx Lap. + GnRH for 9 months + second observation Lap. Tx	15 (55.6%)	- (After 3rd Look Lap., all remained 12 persons candidate for Laparotomy)	27	27	10 (37.04%)	Lap. direct observation and then Lap.	13 (48.1%)
Total	218 (100%)	-	-	Cured by above procedure = 182 (83.5%) Total cured by second and third observation and additional GnRH = 204 (93.6%)	45 (20.64%)	29 (13.3%)	169 (77.52%)	-	47 (21.6%)

GnRH, gonadotropin-releasing hormone; Tx, treatment; Lap., laparoscopy.

patients with stage-IV. Further 3 months medication could reach this rate to 95.3%. The curative rate of the combinational therapy in the stage-IV was 55.6% in the first

step of the protocol. It must be noted that, the process was different in the stage-IV and the initial laparoscopy was only diagnostic and not any procedure for adhesion removal nor other manipulation had been done. The long medication duration for 9 months performed and in the second laparoscopy the adhesions had been removed and spots been electro-cauterized.

Relapse of the endometriosis is a common phenomenon that increases by the severity of the disease. Overall relapse rate of the patients in this study was 21.6%. The relapse rates in the stage I to IV were 10.5%, 22.2%, 23.3% & 48.1% respectively.

It is worth mentioning that only menopausal symptoms (such as hot flashes, sleep disturbance, mood swings, and amenorrhea) were observed in patients during the medical treatment phase. There were no reports of any other symptoms, complications, or complaints during our follow-up.

4. Discussion

This investigational protocol consists of consecutive laparoscopies and time-managed injections of GnRH agonist with a minimally invasive surgical procedure. Furthermore, the treatment duration of the GnRH agonist injection varies between 3 - 12 months depending on the stage of endometriosis. No medical drug treatment was initiated before surgery in our survey because laparoscopy is the gold standard for endometriosis diagnosis, especially in early stages of endometriosis [32] [33]. Although laparoscopy is a definite treatment for endometriomas, the current guidelines for endometriosis removal vary with different approaches [34] [35]. For instance, radical operations on the urinary tract or bowel excision and the resulting inflammatory reactions are the most harmful side effects, which may also cause additional adhesions and endometriosis recurrence themselves. Therefore, some studies suggest avoiding these kinds of operations in endometriosis treatment [35] [36].

The surgical approach in our protocol was a laparoscopic procedure aimed at minimizing the disease symptoms in reproductive organs without any radical manipulations, especially in the visceral organs or bladder. Furthermore, the endometrioma fibrotic capsules were completely drained and extirpated from the ovarian tissue in all cases and because of the risk of ovarian tissue damage with very large endometriomas [37]. The remaining ovarian tissue was sutured to enhance its aggregation [38]. The 3-month GnRH agonist treatment was inadequate for stage III and IV endometriosis [39], and the beneficial effect of a 6-month course of GnRH agonist treatment after laparoscopy [40] was demonstrated. This was evident from the results showing that the subsequent time-managed medical phase of our advanced protocol, which includes various periods of GnRH analog injection after the laparoscopy (depending on endometriosis stage), adequately compensated for the laparoscopic shortcomings based on the high cure rate of the patients.

Interestingly, the symptoms of infiltrative bowel or visceral endometriosis were totally eliminated by the medical drug treatment alone, which was further confirmed by the clinical examinations and the second or third laparoscopic observations. Therefore, as previously recommended, [8] [41], the administration of a GnRH agonist after laparoscopic surgery should be considered as an important part of the endometriosis cura-

tive therapy strategy and recurrence prevention. Consequently, this study demonstrated that compared to all other existing methods, our developed surgical-medical protocol has an acceptable rate of endometriosis removal (93.6%). Therefore, it would be a valuable method for curing endometriosis and preventing its recurrence, particularly for patients who desire to conceive and are referred to an infertility clinic. In addition, we advise patients who do not desire to conceive to take prolonged OCP therapy. Our results also suggest that this advanced method of early definitive diagnosis of endometriosis by performing laparoscopy instead of blindly administering initial medical and drug therapies would be a clinical advancement for endometriosis treatment and related infertility.

In this study we were facing some practical and ethical limitations like the needs for follow-up of the patients, commitment of the patients to the treatment protocol & restriction about the second laparoscopic view in patients with stage-I and third look for patients with stage-II for direct observation as a reliable method for detecting curing the endometriosis lesions.

5. Conclusion

Our present study proved that the severe stage of endometriosis required aggressive and longer treatment duration than the earlier stages did. In addition, we demonstrated that the patients in stage IV required a very complicated treatment regimen of 9 months of decapeptyl injections and extensive laparoscopy or laparotomy surgery. In stage I, we recommended the use of a 3-month course of decapeptyl injections in addition to cauterizing the endometriosis spots using electrocoagulation to achieve a complete recovery. In stages II and III, after the laparoscopy surgery, decapeptyl was injected for 6 months, and the prescription of the new dosage was dependent on the second observational laparoscopy following this period. However, the selection of the best treatment strategy for patients with endometriosis and infertility issues requires additional research and discussion.

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