Comparison of the effect of gonadotropin-releasing hormone agonist and dopamine receptor agonist on uterine myoma growth

Histologic, sonographic, and intra-operative changes

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ABSTRACT

الأهداف: التحقق في أثر العقارين: عقار ديفيريلين وعقار جابرجولين على نمو الورم العضلي الرحمي الأملس والمتغيرات النسيجية، التصويرية والمتغيرات داخل العملية الجراحية.

الطريقة: كجهود لمعالجة الورم العضلي الرحمي الأملس الكبير لدى المريضات اللواتي يعانين من الأعراض ويراجعن عيادة النساء – مستشفى الزهراء التعليمي لجامعة تبريز للعلوم الطبية – تبريز– إيران، خلال الفترة ما بين سبتمبر 2007م وحتى نوفمبر 2008م، تم تقسيم عدد 60 مرشحة بشكل عشوائي لتلقي عقار ديفيريلين بمقدار (3.75mg) أربع مرات كل 28 يوم، وعقار جابرجولين (0.5) مرة واحدة في الأسبوع لمدة ستة أسابيع. تم تقييم الأعراض السريرية، التسليخ داخل العملية، المضاعفات داخل العملية الجراحية والصفات التصويرية والمرضية للورم.

النتائج: خضع عدد 13 مريضة من مجموعة عقار ديفريلين، و10 مريضات من مجموعة عقار جابرجولين للعملية الجراحية. كان هنالك فرقاً ملحوظاً بين المجموعتين في معدل ترشيح الخلايا اللمفية (p=0.003)، إلا أنه لم يكن هناك فرقا في السمات المرضية. في كلتا المجموعتين، بلغ مدخل الانقسام الفتيلي بين (10–0). بينما لم يكن هنالك فرقاً ملحوظاً بين المجموعتين في العدد (p=0.30)، وفي حجم الورم العضلي الأملس (p=0.65)، ولكن كان التغيير في دورة الشريان الرحمي ملحوظا (p=0.001 group I, p=0.026 group II) على التوالي، بالإضافة إلى انه كان هنالك فرقاً ملحوظاً بين المجموعتين في النزف داخل أثناء العملية الجراحية والإلتصاقات للورم العضلي الأملس لجدار الرحم.

خاتمة: تبين أن عقار جابرجولين فعالية كفعالية عقار ديفيريلين في تقليص الورم العضلي وهما متفقين في تطوير النتائج التصويرية، السريرية والنتائج داخل العملية بدون أي تغيرات مرضية عكسية، ويعد كعلاج طبي جيد وإلحاقي للعلاج الجراحي.

Objectives: To investigate the effect of 2 medications; Diphereline and Cabergoline, on uterine leiomyoma growth, and its histologic, sonographic, and intra-operative changes.

Methods: In an effort to treat large uterine leiomyoma in symptomatic patients in the Gynecology Clinics of the Alzahra Teaching Hospital of Tabriz University of Medical Sciences, Tabriz, Iran, from September 2007 to November 2008, 60 candidates randomized to receive Diphereline 3.75 mg, 4 times every 28 days (group I), and Cabergoline 0.5 mg, once a week for 6 weeks (group II), were included in this study. Clinical symptoms, feasibility of intra-operative dissection, intraoperative complications, sonographic, and pathologic characteristics of the tumor were evaluated.

Results: Thirteen patients from group I, and 10 patients from group II underwent surgery. There was a significant difference between the groups in the rate of lymphocyte infiltration (p=0.003), but not in other pathologic features. In both groups, the mitotic index was between 0-10. While there was no significant difference between the groups in the number (p=0.30), and volume of leiomyomas (p=0.65), however, changes in the uterine artery circulation was significant (p=0.001 [group I], p=0.026 [group II]). In addition, there was a significant difference between the groups for intra-operative hemorrhage and adhesion of leiomyomas to the uterine wall.

Conclusion: This study found that Cabergoline is as effective as Diphereline in the shrinkage of myomas, accompanied by improvement in the sonographic, clinical, and intra-operative outcomes without any adverse pathological changes, and could be a good medical regimen as an adjunct to surgical management.

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Uterine leiomyoma, a benign smooth muscle tumor, may sometimes causes infertility, and significant morbidity.[1,2] A number of reviews have tried to show the ethological factors, but the cause, and the exact biology of this tumor is yet unknown.[3-6] Sex hormones, growth factors, and cytokines may play a key role in the formation of leiomyomas.[3-10] It seems that continuous estrogen secretion is the most important predisposing factor.[11-13] Yamamoto et al[14] had reported that the concentration of estrone and estrone sulfatase activity in the endometrium overlying a myoma is high.[14] Others showed a possible role for the 5α-reduced androgens,[15] chemokines, retinoic acid,[16] and genistein.[17] Some of the reviewed studies have shown abnormalities in the endocrine and the pituitary function.[18,19] In addition, a role has been suggested for the regulatory factors,[20] polypeptide growth factors, and prolactin.[21,22] A single gene involved for commonly occurring uterine fibroids has not been detected.[23] The investigations have not also demonstrated a definite role for tumor suppressor genes.[24] By understanding the molecular biology and the genetics of the leiomyoma, there is a tendency to develop newer nonsurgical therapies.[25,26] Trials of pre-operative medical management indicate that these medications could reduce the fibroid volume, but do not provide sufficient evidence of improvement in the important operative outcomes.[2] However, there is no new definitive evidence around the pathologic changes that may result from different medical therapies. Histologic evidence of extensive degenerative changes in leiomyoma has been reported by long-acting progesterone therapy.[27] Pathologic changes were also reported in patients who have received gonadotrophin-releasing hormone agonists (GnRHa).[28] Nakayama et al[29] reported an increased number of mast cells after GnRHa therapy. There is probably a greater emphasis on the expectant and conservational management of uterine myoma in the future. The GnRHa has been successfully administrated to reduce tumor size, the levels of ovarian hormones, and a number of growth factors.[30-32] While this strategy could facilitate the route and manner of surgery,[33] it may result in complications, or life-threatening conditions.[34] The administration of progesterone was also disappointing.[35] In contrast, antiprogestin therapy with mifepristone (RU-486) has been shown to be effective.[36] Recently, new treatment options targeted growth factors, and proved to be useful. The role of growth factors, including prolactin in the development of the uterine leiomyoma is under way. Prolactin has various forms and functions. The prolactin receptor belongs to a receptor family that includes many cytokines and many growth factors, which supports a dual role for prolactin as a classic hormone, and as a cytokine.[37] It is noteworthy, that the only treatment strategy for uterine leiomyoma is surgery. Leiomyomas, especially its mitotically active variant, produce growth factors, which are able to stimulate tumor growth by the autocrine mechanism.[38] By clarifying the role of growth factors in the growth of the leiomyoma, the treatment targeted at the growth factor, or its receptor can prove useful. We have previously shown that Cabergoline (a dopamine agonist), was effective in the shrinkage of myoma, and other clinical outcomes.[39] The aim of this present study is to compare the effect of GnRHa (Diphereline) and the dopamine receptor agonists (Cabergoline) on the uterine myoma growth, and its histologic, sonographic, intra-operative changes, and side effects, and to explore their association with tumor shrinkage, and degeneration caused by therapy.

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Methods. In a single blinded randomized clinical trial, which was carried out in the Gynecologic Clinics of Alzahra Teaching Hospital of Tabriz University of Medical Sciences, Tabriz, Iran, from September 2007 to November 2008, 60 women with uterine leiomyoma, who met the criteria of the study thoroughly, were included. Entry criteria were women of reproductive age who had abnormal uterine bleeding, or infertility with uterine intramural myomas. Patients with submucous or subserous myomas, ≥43 years old were excluded. Patients who had abnormal uterine pathology, and infection, were also excluded. The study was approved by the regional Medical Research Ethics Committee of Tabriz University School of Medicine. Medications were started according to our previous study,[39] and the same evaluation criterion was used. After informed consent was obtained, eligible participants randomly took one of the medications. Similar to our previous study,[39] for the first group (group I), 3.75 mg of GnRHa (Diphereline [IPSEN Pharma Biotech, Paris, France) was prescribed 4 times every 28 days, and for group II, 0.5 mg of Cabergoline (Dostinex, Pharmacia and Upjohn SPA, Milan, Italy), was prescribed once a week for 6 weeks. Evaluation criteria included the frequency and duration of uterine bleeding, pelvic pain, bone sensitivity and pain, hot flushes, and psychological symptoms. The results of the pelvic examination and the abdominovaginal sonographic findings before and after the treatment, were documented. In patients with multiple leiomyoma, the largest one was selected. Follow-

up visits were carried out one week after the termination of medical treatment, and sonography was conducted at this time, to assess the rate of myoma shrinkage. More than 20% reduction in the tumor volume was deemed a good response. In addition, in each group, before and after treatment, changes in the clinical symptoms and the uterine artery circulation was evaluated. Thirteen patients from group I, and 10 patients from the group II underwent surgery according to clinical symptoms. The feasibility of intra-operative dissection, intraoperative complications, and the pathologic characteristic of leiomyomas were compared. The range of adhesion was recorded as mild, moderate, and severe.

Data were entered into the computer and Kolmogorov-Smirnov statistics were used for testing the normality of continuous variables. Data analyses included independent and paired samples t test, repeated measurements of ANOVA for the continuous variables, and Chi-square, or Fisher exact test for categorical variables. Data are expressed as mean ± standard deviation. A *p*-value of <0.05 was considered statistically significant. All statistical procedures were performed using SPSS version 14.0 for Windows.

Results. Demographic and obstetrical characteristics are shown in **Table 1**. The results of marital status are reported in the simple percentage form, and Fisher's exact test showed no significant difference between groups (χ^2=0.80, df=1, p=0.27). Eighty percent of patients in group I (n=24), and 70% of patients in group II (n=21) had been married, and the number for unmarried groups were 20% for group I (n=6), and 30% for group II (n=9). The effect of treatment on myomas is shown in **Table 2**. The tumor regressed significantly in both groups, and there was no significant difference between group in the mean uterine volume, before and after the intervention (p =0.65) (**Figure 1**). In addition, the results of Fisher's exact test showed no significant difference between groups in the number of myomas, before and after the treatment (p=0.30) (**Table 2**). The results of repeated measures of variance show that the changes in the duration of hemorrhage in both groups were statistically significant (p=0.0001), and these changes in group I was more than in group II (p=0.016) (**Table 2**) (**Figure 2**). The results of this test for the cycle length in both groups were also significant (p<0.0001). In addition, within the groups, the difference at the cycle length changes was significant (p=0.001) only in group I (**Table 2**) (**Figure 3**). In group I, pelvic pain was relieved in 5 cases after the treatment, and did not change in 11 cases. There was no pain in 14 cases before, and after the treatment in this group. In group II, pelvic pain was relieved in 5 cases after the treatment, and did not change in 11 cases. There was no pain in 12 cases before, and after the treatment. In 5 cases, the patient's despite being painless before the treatment, experience pain afterward. In addition, statistical comparison between groups in the range of skeletal pain and tenderness before, and

Table 1 - Demographic and obstetrical characteristics.

Variables	Group I	95% CI	Group II	95% CI	t	df	*P*-value
Age (years)	39.67 ± 8.62	36.06-42.76	36.87 ± 6.74	33.60-39.90	1.40	58	0.16
Gravidity	2.70 ± 0.46	1.54-3.62	2.27 ± 0.44	1.38-3.12	0.67	58	0.50
Parity	2.57 ± 0.45	1.46-3.46	1.87 ± 0.41	1-2.50	1.14	58	0.25

CI - confidence interval, t - paired t test, df - degrees of freedom, p<0.05 was considered significant

Table 2 - Characteristics of clinical variables and myoma changes in participants who took Diphereline and Cabergoline before and after treatment.

Demographics	Group I Mean ± SD (95% CI)		Group II Mean ± SD (95% CI)		t	df	*P*-value
	Before	After	Before	After			
Menstrual duration (days)	13.03 ± 5.43 (10.66 - 14.96)	6.87 ± 7.88 (2.82 - 8.34)	10.77 ± 5.98 (7.69 - 11.98)	8.60 ± 5.50 (5.65 - 9.54)			0.016
Cycle length (days)	15.60 ± 8.66 (12.95 - 19.82)	9.00 ± 11.13 (4.89 - 14.34)	20.57 ± 7.78 (16.66 - 23.26)	23.40 ± 7.61 (20.87 - 26.96)			0.001
Number of myomas	1.47 ± 0.77 (1.13 - 1.64)	1.50 ± 0.77 (1.13 - 1.64)	1.73 ± 0.86 (0.88 - 2.45)	1.63 ± 0.96 (1.04 - 2.12)	1.07	58	0.30
Mean tumor volume (mm^3)	376.53 ± 40.46 (275.26 - 464.12)	289.29 ± 40.31 (191.51 - 363.10)	364.83 ± 46.14 (241.43 - 459.07)	278.13 ± 47.50 (204.17 - 424.25)	0.66	58	0.17
Mean tumor volume changes (mm^3)	113.13 ± 34.34 (95.36 - 146.18)		86.70 ± 48.9 (67.27 - 120.47)		0.44	58	0.65

95% confidence interval (CI), SD - standard deviation, df - degrees of freedom, t - paired t test, p<0.05 was considered significant

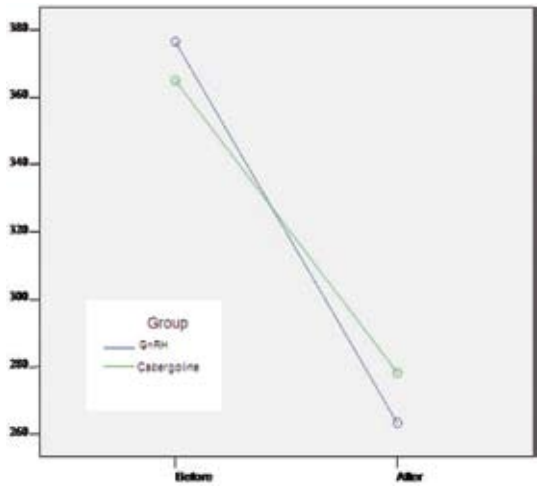

Figure 1 - Myoma volume changes (ml), before and after intervention. GnRH - gonadotropin-releasing hormone

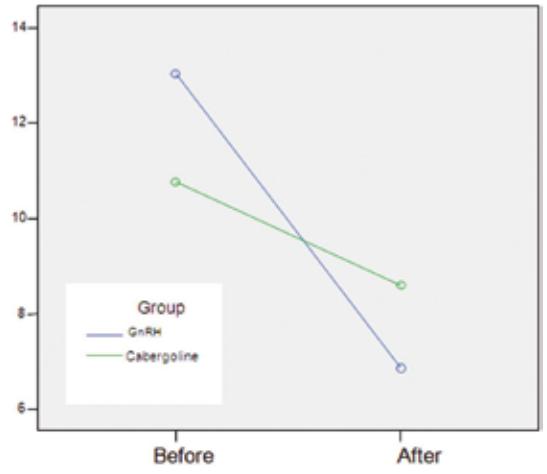

Figure 2 - The changes in the menstrual duration, before and after intervention. GnRH - gonadotropin-releasing hormone.

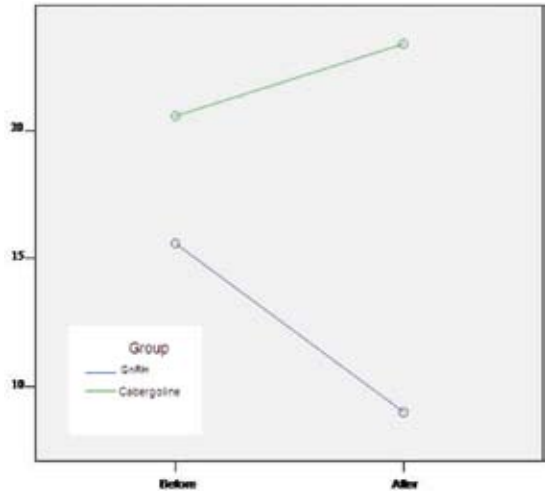

Figure 3 - The changes in the menstrual cycle length, before and after the intervention. GnRH - gonadotropin-releasing hormone.

after the treatment showed significant difference only in group I (**Table 3**). The results of hot flushes before, and after the treatment is also shown in **Table 3**. Hot flushes were experienced by more than 66% of the patients, usually in 1-6 weeks after starting with Diphereline. In group II, 73.3% of patients had no hot flushes before and after the treatment, and 16% of patients experience hot flushes, 1-6 weeks after beginning the treatment. Both interventions statistically had no significant effect on hot flushes (**Table 3**). The results showed that in group I, vaginal dryness was present in 11 cases before, and 11 cases after the treatment. The results are the same in group II, 0% before and 13% after the treatment. The same results for the absence of vaginal dryness before (19 cases), and after (19 cases) treatment for group I, and 30 cases before, and 17 cases after treatment for group II. Other clinical characteristics of the patients are shown in **Tables 4** and **5**. The participant's mean uterine artery circulation were 0.72 ± 0.11 before, and 0.76 ± 0.11 after treatment in group I (p=0.001), and 0.69 ± 0.08 before, and 0.75 ± 0.05 after the treatment in group II (p=0.026), which was significant. Group II had few intraoperative complications compared to group I (p=0.03). In group I, dense adhesion was more than in group II. There was no severe adhesion of leiomyoma to the uterine wall in group II. In group I, moderate adhesion (76.9%) was more than in group II (20%), and the feasibility of dissection in group I compared to group II was less. There was also a significant difference between groups for intraoperative hemorrhage (p=0.03) (**Table 6**). Unusual morphologic features of leiomyomas were seen in patients who had been treated preoperatively with Diphereline, such as vasculitis and massive lymphoid infiltration. The rate of vasculitis in group I was 43.3%, and 33.3% in group II. In group I, mild (12 cases), moderate (one case), and severe hyalinization (0 case) was seen, and in group II there were 4 cases (mild), 2 cases (moderate), and 4 cases (severe hyalinization) was observed. There was a significant difference between groups in the rate of lymphocyte infiltration (p=0.003), but there was no significant difference in the rate of vascular density (p=0.43), vascular thrombosis (p=0.9), tissue cellularity (p=0.69), and necrosis (p=0.43). The vascular thickness and cellular density was normal in both groups, and the mitotic index was between 0-10 (**Table 7**).

Discussion. Uterine leiomyoma is a common women's health problem during the reproductive age.[1] It is estimated that the lifetime risk of fibroids is 50-80%.[2,40,41] However, its true incidence and prevalence was not determined accurately.[42] Studies have shown that with increasing age, the effect of fibroids on the reproductive health and well-being worsens, and the need for surgical interventions is increased.[43,44] Both

Table 3 - The results of participant's skeletal tenderness, pain, and hot flushes, before and after treatment.

Characteristics	Group I		Group II		χ^2	df	*P*-value
	Before	After	Before	After			
Hot flushes$^+$	1	20	2	7	0.44	1	0.14
Hot flushes$^-$	29	9	27	5	2.49	1	0.12
Pain and tenderness$^+$	3	16	5	4	2.54	1	0.23
Pain and tenderness$^-$	14	14	25	24	17.32	1	0.001

+: present, -: absent, χ^2 – Chi-square test, df - degrees of freedom, *p<0.05 was considered significant

Table 4 - The results of participant's psychologic symptoms, before and after treatment.

Characteristics	Group I		Group II		χ^2	df	*P*-value*
	Before	After	Before	After			
Psychologic symptoms$^+$	2	2	1	3	30	1	0.002
Psychologic symptoms$^-$	28	28	29	27	9.31	1	0.10

+: present, -: absent, χ^2 – Chi-square, df - degrees of freedom, *p<0.05 was considered significant

Table 5 - Clinical characteristics of patients, before and after treatment.

Parameters	Before treatment	After treatment	χ^2	df	*P*-value
Muscular stiffness (group I)*	0.0	0.0	-	-	-
Muscular stiffness (group II)*	0.0	1.0	-	-	-
Muscular depression (group I)	4.0	7.0	6.72	1	0.13
Muscular depression (group II)	2.0	5.0	10.71	1	0.02
Electrical shock	0.0	1.0	-	-	-
Nausea (group I)*	6.0	12	-	-	-
Nausea (group II)*	0.0	0.0	-	-	-
Vomiting (group I)*	0.0	2.0	-	-	-
Vomiting (group II)*	0.0	0.0	-	-	-
Positive feeling of dizziness (group I)	0.0	0.0	1.01	1	0.5
Positive feeling of dizziness (group II)	1	8	9.23	1	0.002
Treatment continuity, drug (group I)*		10	-	-	-
Treatment continuity, surgical (group I)		13	0.63	1	0.29
Treatment continuity, drug(group II)*		20	-	-	-
Treatment continuity, surgical (group I)*		10	-	-	-

*In these circumstances there was limitation to perform statistical analysis to show the differences or associations, χ^2 – Chi-square test, df - degrees of freedom, p<0.05 was considered significant

Table 6 - Results of intra-operative variables in participants who took Diphereline and Cabergoline, before and after treatment.

Variables	Group I Mean ± SD (95% CI)	Group II Mean ± SD (95% CI)	t	df	*P*-value
Number of gases	7.33 ± 1.62 (2.89 - 9.80)	2.30 ± 0.68 (0.51 - 3.91)	2.86	38.99	0.007
Number of long gases	3.40 ± 1.77 (1.25 - 4.44)	1.03 ± 0.40 (0.11 - 1.47)	2.71	44.07	0.009
Suctioned blood (cc.)	93.33 ± 22.58 (30.44 - 123.41)	44.33 ± 12.68 (5.93 - 59.07)	1.89	45.63	0.03

CI - confidence interval, t - paired t test, df - degrees of freedom, p<0.05 was considered significant

patient and gynecologist can make a proper decision for creating a treatment plan, based on patient's symptoms, and desire. According to the new evidence-based studies on the management of uterine fibroids, there is a significant research gap between well-conducted trials, especially long-term outcome studies on the therapies for medical management, and information on treatment decisions for women who desire pregnancy.[2]

To choose a proper method, the gynecologic surgeon must be familiar with its pathology, growth characteristics, and clinical features. Surgical excision by a variety of techniques remains the most effective, and widely used method of management for patients with significant symptoms.[45,46] However, during the past decades, traditional surgical management of uterine myoma was changed, and new surgical approaches, nonsurgical management, and medical approaches have developed.[25,26,47-51] In addition, an effective medical approach which results in the permanent cure of uterine leiomyoma, is not yet available. Hormones had been applied for many years to help improve the outcomes. Trials of preoperative medical management have indicated that treatment reduces fibroid volume, but does not provide sufficient evidence of improvement in important operative outcomes.[2] However, different medication will produce histologic changes that are not examined thoroughly. The GnRHa and progestational agents are among several protocols that have been proposed for myoma regression before surgery, and to control clinical symptoms.[3,22]

Table 7 - Patient's pathologic results.

Parameters	Group I n (%)	Group II n (%)	χ^2	df	*P*-value
Vasculitis	13 (43.3)	10 (33.3)			
Lymphocytic infiltration	2 (15.4)	8 (80)	1.91	1	0.003
Presence of necrosis	0 (0)	1 (10)	1.35	1	0.43
↑Vascular density	0 (0)	1 (10)			
Vascular thrombosis	1 (7.7)	1 (10)			
↑Vascular thickness	0 (0)	0 (0)			
Cellularity, one	10 (33.3)	3 (24.2)	0.67	1	0.69
Vascular lumen size	5 (38.4)	7 (70)	2.25	1	0.21
Cellular density	normal	normal			
Mitotic index	0-10 (100)	0-10 (100)			

↑ - increase, **p*<0.05 was considered significant, χ^2 – Chi-square, df - degrees of freedom.

In our previous study,[39] we examined the effect of a dopamine-receptor agonist (Cabergoline), and a GnRHa (Diphereline) on myoma growth, and noted that Cabergoline had a comparable effect with Diphereline on tumor regression with fewer adverse effects.[39] In the present study, in addition to myoma growth, sonographic characteristics, histologic and intra-operative changes have also been evaluated, and the results were promising, too. The regression of tumor in both volume and number, were comparable between groups with no significant difference (**Table 2**). The mean uterine artery circulation before (p=0.001), and after (p=0.026) the treatment in both groups was significant, and was comparable with the results of other studies.[30]

In one study by Ito et al,[31] instead of measuring volume, they evaluated ultrastructurally uterine leiomyoma cells from the same myoma nodule before and after the GnRH-agonist treatment and found it to be effective. In another study, both RU-486 and leuprolide acetate have been shown to be effective in decreasing the blood flow to the uterus.[52] On the other hand, detection of hypervascularity in combination with other sonographic findings could identify suspicious uterine smooth muscle tumors from myomas.[53,54] Whereas the duration of hemorrhage was reduced in both groups significantly (**Table 2**), however, this changes in group I was more than in group II (**Figure 2**). This may be related to the hypo-estrogenic state and reduction of blood flow as shown in other studies.[55] The cycle length was reduced significantly in group I only (**Figure 3**). The changes at the severity of pelvic pain after treatment was also comparable. However, the range of skeletal pain and tenderness, before and after the treatment was significant only in group II (**Table 3**). The effects on hot flushes in both group were not significant (p=0.14). Like in other studies,[34,56,57] in group I, vaginal dryness was significant, whereas in group II, it was not. Other symptoms of hypogonadal state such as insomnia, mood liability, headaches, arthralgias, and myalgias, were significant only in group I. Similar to group I, pelvic pain, and dysmenorrhea were relieved in women who had received Cabergoline. Group II had few intraoperative complications compared to group I (**Table 6**). Diphereline caused more dense adhesion of myoma to the uterine wall, whereas Cabergoline produced a loose tissue which caused easy dissection. Similar to other studies,[58-61] the amount of hemorrhage during surgery in group II was low, but the feasibility of dissection with dopamine agonist agents was better, and it may be related to the role of these agents on growth factors.[38] A study reported fewer peritoneal adhesions after pretreatment with GnRHa compared with no treatment.[62] In this study, we did not examine this variable.

The morphologic features in group I, such as vasculitis compare to group II was significant (43.3% versus 33.3%), and was comparable with other studies.[63,64] Whereas, there was a significant difference between groups at the rate of lymphocyte infiltration, but there was no significant difference between groups at the rate of vascular density, vascular thrombosis, tissue cellularity, necrosis, mitotic index, and hyalinization (**Table 7**). The vascular thickness and the cellular density were normal in both groups. In an earlier study,[27] an extensive degenerative change after using long-acting progesterone to treat uterine myomas was also reported. In this study, no other variable was evaluated.[27] Recently, investigators had demonstrated that progesterone receptor modulators could induce collagenolysis.[3] Kawamura et al,[65] in a histopathologic analysis related to myoma volume after treatment with GnRHa, found a correlation between shrinkage of uterine myoma and the degree of cellularity, hyaline change, and collagen content of biopsy specimen before treatment. In this study, there was also no specimen after the treatment to compare the effects on the histopathologic features. In another study, Nakayama et al[29] evaluated the pathological changes of uterine myomas in patients who were treated with or without GnRHa, and showed a role for the mast cells, and a possible mechanism of GnRHa resistance in these tumors. They showed that the number of mast cells significantly increased in myomas of patients treated with GnRHa, while insulin-like growth factor I (IGF-I) immunoreactivity was significantly reduced in the smooth muscle cells of these myomas. These observations may provide an explanation for the possible mechanism of GnRHa resistance in myomas.[29] Di Lieto et al[66] evaluated the clinical response, immunohistological expression of the angiogenetic growth factors fibroblast growth factor-(I^{2}FGF, vascular endothelial growth factor, and platelet-derived growth factor), and vascular changes in uterine leiomyomas from women treated with GnRHa. These authors also reported a reduction in the synthesis of these growth factors in myomatous cells, and the total number of vessels and angiogenetic vessels.[66] According to Flierman et al,[67] while preoperative administration of intramuscular GnRHa is associated with a significant reduction in the uterine size,[67] it is not associated with an improvement in the short-, or long-term outcomes, except in improving anemia.[33] As was shown in our study (**Table 6**), while preoperative treatment with GnRH analogs can actually reduce the operative blood loss during myomectomy,[60,68] and decrease in the uterine volume through the induction of cell damage,[31] but such damage can be just sublethal and reversible.[32,69,70] However, when the GnRHa was administrated for a long time, it may be irreversible.[71] Despite the uterine artery circulation before (p=0.001), and after the treatment (p=0.026), however, intraoperative hemorrhage and bloodless operative field, were less in Group II (**Table 6**). In patients who were treated with GnRH analogs, the plane of cleavage may seem less distinct. Sharp dissection with the scalpel or Metzenbaum scissors, or blunt dissection with the finger or knife handle, is required to inoculate the myoma from its bed. This effect could be related to the blood flow changes,[72] or high concentrations of collagen-associated amino acids in the uterine wall. These changes are usually obscured ultrasound outline.[73] In our study, the plane of cleavage between the myoma and the surrounding myometrium, and identifying the dissecting plane in group II was easier than in group I. Ultrasonic outline, however, was not evaluated in our study. In myomas that were exposed to the GnRHa, blood flow reduction, and not hormonal depletion may cause tumor shrinkage.[72] Whereas, in Group II, hormonal effect maybe responsible for myoma shrinkage.

Cabergoline may have an antiproliferative effect on leiomyoma cells via membrane receptors for prolactin.[37,38] These agents was suggested to be used as a novel treatment modality for the treatment of leiomyoma. However, due to the relatively small sample size, the results obtained here are suggestive, and additional studies with larger sample size are needed to increase the validity of the findings. It is a dream for most women who have uterine myoma to wake up one morning, and realize their tumor completely gone.

Prophylactic therapy has not been suggested to prevent future complications.[74] Close observation of women with uterine leiomyomas is recommended, and intervention is reserved for specific indications and symptoms as shown in other studies.[46]

In conclusion, the results show that Cabergoline is effective as GnRHa in the shrinkage of myomas, accompanied by improvement in clinical, intra-operative, and sonographic outcomes without any adverse pathological changes, and could be a good medical regimen to improve clinical outcomes, or as an adjunct to surgical management. This information regarding hormonal therapy in patients with uterine myoma is promising, however, patients should be made aware that limited long-term data are not available regarding outcomes, especially relating to fertility and pregnancy, but in light of short outcomes such as pain relief, myoma size reduction, intra-operative complications, and uterine circulation improvement, dopamine agonists may hold promise as a novel treatment strategy for leiomyoma.

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