

A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: Efficacy and ultrasonographic predictors

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OBJECTIVE: Aims of our study were as follows: (1) to evaluate the therapeutic efficacy of the preoperative administration of a gonadotropin-releasing hormone analog before laparoscopic myomectomy and (2) to assess whether any ultrasonographic parameter of the fibroids (number, size, Doppler velocimetry, or echogenicity) was of prognostic value.

STUDY DESIGN: A prospective randomized study was performed on 67 patients with symptomatic uterine fibroids that were mainly intramural; these patients were undergoing laparoscopic myomectomy. Patients were randomized either to preoperative administration of two injections of a depot formulation of leuprolide acetate 28 days apart (group A, $n = 35$) or to direct surgery (group B, $n = 32$). In each group we studied the number, volume, and echogenicity of the larger fibroids; the resistance index of uterine arteries and of fibroid vessels; hematologic parameters; operative time; and blood loss.

RESULTS: The two groups did not differ significantly in basal ultrasonographic parameters and hematologic data. Postoperatively, the red blood cell count and the serum hemoglobin and iron levels were significantly ($p < 0.05$) lower in group B. Both blood loss ($p < 0.01$) and operative time ($p < 0.05$) were significantly lower in group A. However, the operative time was significantly longer when the main fibroid was markedly hypoechoic, probably because the increased softness of the tumor after leuprolide acetate pretreatment makes its enucleation much more cumbersome.

CONCLUSION: Our data confirm the therapeutic efficacy of preoperative administration of a gonadotropin-releasing hormone analog before laparoscopic myomectomy in reducing the blood loss and in decreasing the operative time. This preoperative course of leuprolide acetate in hypoechoic fibroids, because of the further reduction of the density of the myomas, causes a significant ($p < 0.05$) increase in operative time. (*Am J Obstet Gynecol* 1998;178:108-12.)

Key words: Leuprolide acetate, laparoscopic myomectomy, uterine fibroids

Although still controversial,¹⁻⁵ laparoscopic myomectomy is becoming increasingly more common for the treatment of symptomatic intramural fibroids, probably because laparoscopic surgeons are becoming more proficient in intracorporeal suturing.

A logical attempt to make this type of surgery easier and faster is to reduce the myoma size and the blood flow to the uterus⁶ by means of preoperative gonadotropin-releasing hormone (GnRH) analog therapy. However, preoperative GnRH analog treatment has been reported to cause an increased risk of recurrence,⁷ a possible delay in

the diagnosis of leiomyosarcoma,⁸ a risk of massive hemorrhage from degeneration,⁶ a greater difficulty in finding the cleavage plane,⁹ and a greater extent of hyalinization phenomena.¹⁰ Nevertheless, the reduction of myoma volume and the decreased vascularity of the uterus may represent important factors in facilitating laparoscopic myomectomy and improving results.^{11, 12}

To assess the therapeutic efficacy of the preoperative GnRH analog treatment in laparoscopic myomectomy, we conducted this prospectively randomized study in 74 patients with symptoms who were scheduled for myomectomy. We compared the operative time, the blood loss, and the hematologic parameters between the two groups, and we correlated the results with the preoperative ultrasonographic findings.

Material and methods

From September 1994 to July 1996, 74 women with symptomatic uterine fibroids, who were referred to the Department of Gynecologic and Pediatric Sciences of the University of Reggio Calabria and to the Endogyn

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Service Private Center for Endoscopic Surgery in Naples and who were shown to fit the entry criteria, were included in the randomized trial. The study was approved by the Department Ethical Committee, and written informed consent was obtained from each patient.

Inclusion criteria were (1) history of infertility lasting >3 years or recurrent abortions; (2) symptoms of increased vaginal bleeding, pelvic pain, or pelvic pressure; (3) lack of pedunculation of the main myoma with an ultrasonographic size <500 cm³ but >4 cm³; (4) presence of no more than four myomas per patient; (5) absence of submucosal fibroids as screened by hysteroscopy; (6) absence of ultrasonographically documented calcification in the main myoma; (7) absence of hyperplasia with cytologic atypia in the endometrial biopsy performed because of menometrorrhagia; (8) absence of abnormal Papanicolaou smear; and (9) negative urine pregnancy test result.

The enrolled patients were allocated to one of the two groups according to the same computer-generated random assignment for both centers: Group A received the GnRH analog pretreatment and group B underwent direct surgery.

In group A two intramuscular injections of leuprolide acetate 3.75 mg (Enantone, Takeda, Rome) were administered to each patient 4 weeks apart starting in the luteal phase or within the first 2 days of menses, and the laparoscopic myomectomy was performed 2 to 5 weeks after the second injection.

Ultrasonographic evaluations of uterine volume and the number and volume of the myomas were performed with an Aloka SSD 680 (Aloka Co., Tokyo) device with either a 3.5 MHz transabdominal transducer or a 5 MHz transvaginal probe by means of the ellipsoid formula $D1 \times D2 \times D3 \times 0.5233$ (D1, D2, and D3, respectively, were the length and the transverse and anteroposterior diameters).

A pulsed-wave duplex system with the same sector scanner and a high-pass filter of 100 Hz was used to obtain the blood flow velocity waveforms of uterine arteries and, when possible, of the major vessels supplying identifiable fibroids. The peak systole (*A*) and peak diastole (*B*) were measured to calculate $(A - B)/A$ the resistance index, with the mean values of three consecutive measurements taken into account and a coefficient of variation of 2% to 4%.

The echogenicity of the main fibroid was evaluated by means of a relative score of 1 to 7, with 5 considered as isoechoic to the surrounding myometrium.

All of the above-cited ultrasonographic determinations were performed on admission of the patient into the study (T0) and in group A immediately before surgery (T1). A complete blood cell count with differential count and the serum hemoglobin and iron levels were obtained at admission (T0), before surgery (T1), and 1 week after surgery (Tf).

Laparoscopic myomectomy was performed by use of a 10 mm scope (Karl Storz, Tuttlingen, Germany) with two or three ancillary ports. The first step was always the infiltration of the fibroid base with up to 20 ml of octapressin (Por-8, Sandoz, Basel, Switzerland) 5 IU in 1 ml diluted 1:30 followed by a longitudinal, possibly close to the midline, unipolar or hook scissors incision. After the identification of the cleavage plane, the fibroid was enucleated by means of adequate traction with a myoma drill or a strong grasper and counter traction maneuvers with Manhes forceps, scissors, or hydrodissection instruments. Coagulation of significant bleeders was obtained with bipolar forceps, and the myometrial edges were reapproximated in one or two layers according to the depth of the uterine wound, by means of Vicryl CT 2-0 (Ethicon SpA, Pratica di Mare, Rome) polyglactin interrupted figure-of-eight sutures. The fibroids were removed in 41 cases with a 15 mm Semm (Wisap, Sauerlach, Germany) morcellator¹³ and in the remaining 26 cases with a 12 mm Steiner (Karl Storz) automatic morcellator.¹⁴

At surgery (Ts) the entire operative time was noted. The blood loss was evaluated as the balance between the aspirated fluid and the irrigated liquid. In all cases operative samples were submitted for pathologic examination.

All randomized patients recruited for the study for whom data were available were included in the efficacy analysis. Statistical significance of between-group comparisons was assessed by χ^2 test for proportions, and the Student *t* test for paired data has been used for comparison of data between T0 and T1. The Student *t* test for unpaired data has been used for comparison between groups A and B, when appropriate. Duration of operation and intraoperative blood loss were analyzed with the Wilcoxon rank-sum test. Furthermore, for multiple comparison an analysis of variance with repeated measures was used. The power analysis of the study is reported at the beginning of the Comment section. In all analyses statistical significance was assessed at the 5% level.

Results

At the time of laparoscopy 7 cases (2 in group A and 5 in group B) were excluded from the study either because the main fibroid was pedunculated or <4 cm³ in volume or because there was an association with severe adhesions or endometriosis.

The 67 patients included in the study were aged 24 to 45 years (mean \pm SD 37.2 \pm 4.0), with a parity range of 0 to 3 (mean \pm SD 1.4 \pm 0.6) and a weight range of 55.4 to 79.6 kg (mean \pm SD 63.6 \pm 4.7).

At admission (T0) the two groups were not different in age, parity, weight, and indications to surgery (Table I). Uterine volume, number of fibroids, volume of main fibroid, echogenicity of main fibroid, resistance index of uterine arteries, resistance index of main fibroid vessels, red blood cell count, and serum hemoglobin and iron

Table I. Patients' characteristics

| Characteristic | Group A (n = 35) | Group B (n = 32) | Significance |
|---------------------------------|---------------------|---------------------|--------------|
| Age (yr, mean \pm SD) | 36.8 \pm 4.1 | 37.7 \pm 3.9 | NS |
| Weight (kg, mean \pm SD) | 64.4 \pm 4.6 | 62.8 \pm 4.4 | NS |
| Parity (mean \pm SD) | 1.4 \pm 0.7 | 1.5 \pm 0.5 | NS |
| Indication for myomectomy (No.) | 15 (42.8%) | 10 (31.2%) | NS |
| Abnormal uterine bleeding | 8 (22.9%) | 9 (28.1%) | NS |
| Infertility | 7 (20.0%) | 6 (18.8%) | NS |
| Abortion | 5 (14.3%) | 7 (21.9%) | NS |
| Pain | | | |

NS, Not significant.

levels were not significantly different between groups at admission (Table II).

In group A the two injections of GnRH analog significantly reduced the uterine volume, the volume of the main fibroid, and the echogenicity of the main leiomyoma. The number of fibroids found at the time of admission ultrasonography was always confirmed at the time of laparoscopy. The uterine arteries and the resistance index of the main fibroid vessels were significantly increased preoperatively, proving that the flow was decreased after leuprolide treatment (Table II).

Postoperatively, the red blood cell count and the serum hemoglobin and iron levels were lower in group B. Both blood loss and operative time were significantly lower in group A ($p < 0.01$ and $p < 0.05$, respectively) (Table III).

The extraction time was significantly shorter in those cases in which the Steiner morcellator was used in both group A and group B (12.2 ± 8.1 vs 19.8 ± 12.3 , $p < 0.05$), but the cases in which the automatic morcellator was used were equally distributed between the two groups (13 cases in group A and 13 in group B).

Among the ultrasonographic parameters evaluated at admission any significant difference in the operative parameters was shown to be related to the Doppler velocimetry of uterine vessels and the major vessels of the main fibroid.

Both more than two myomas and main fibroid volume greater than 60 cm^3 showed a significant improvement in the operative time when pretreated by a 2-month course of GnRH analog (Table IV). Particularly interesting are the surgical correlations of the parameter echogenicity of the main fibroid. The cases with a basal fibroid echogenicity of <3 showed a significantly ($p < 0.01$) longer surgery time after treatment with a GnRH analog than was found for the rest of the pretreated fibroids or the untreated patients (group B) with hypoechoic myomas (Table IV).

We had no significant complications and none of the

procedures was converted to laparotomy. We had 4 patients with a transient postoperative fever ($<39^\circ \text{C}$), 2 in each group, and a pelvic mass (hematocele?) $<5 \text{ cm}$ in diameter that developed in one patient resolved spontaneously within 3 weeks. Blood transfusion with 2 units of packed red blood cells was required in one patient from the subgroup of pretreated hypoechoic fibroids.

For all 67 patients we have a clinical follow-up of at least 6 months. Abnormal uterine bleeding occurred in 4 out of 25 patients (16.0%). In patients with infertility or abortion a pregnancy rate of 42.5% (17/40), with an abortion rate of 23.5%, was obtained. Three patients among the infertility group who did not become pregnant underwent a diagnostic microlaparoscopy after 6 months. In 2 of these 3 women filmy adhesions were detected at the site of hysterotomy. Three of the 12 patients (25.0%) referred with symptoms of pelvic pain complained of pain of similar intensity at the 6-month follow-up.

Comment

Uterine fibroids are the most common benign gynecologic tumors but in patients with symptoms they should be removed.¹⁵⁻¹⁸ Currently, laparoscopic myomectomy is still controversial but is becoming more and more common.^{4, 19, 20} The use of preoperative GnRH analog has been advocated in the hope that it may make surgery easier and faster by reducing the myoma size and blood loss. Indeed, previous studies have suggested that the preoperative GnRH course (2 to 3 months) before myomectomies performed by laparotomy has been effective in reducing the blood loss,²¹ especially in patients with uteri $>600 \text{ cm}^3$.²²

The increased recurrence rate associated with GnRH analog⁷ seems to be related more to the number of fibroids²³ than to the preoperative medical treatment. More important, the recurrence rate is not associated with a greater reintervention rate, quoted as low as 10%.¹⁹ Currently, however, there is no report showing the therapeutic efficacy of preoperative GnRH agonist treatment before laparoscopic myomectomy.

In this prospectively randomized study we selected only cases in which the main fibroids were intramural and reconstruction of the uterine walls with sutures was necessary. This selection was necessary to obtain a homogeneous series of cases with comparable surgical difficulty.

The power analysis of this study for the outcome measure "operative time" showed a value of $\beta = 0.898$ with a power of 0.102. Regarding blood loss, the other main outcome parameter, $\beta = 0.939$ with a power of 0.061. Therefore the sample size provided a power $>90\%$ to detect such a difference in comparing the two groups at the 5% significance level.

Our results confirm the feasibility of laparoscopic my-

Table II. Ultrasonographic and hematochemical characteristics

| | Group A (n = 35) | | Group B (n = 32) |
|--|--------------------------|-------------|------------------|
| | T0 | T1 | T0 |
| Uterine volume (cm ³) | 473 ± 88 [†] | 396 ± 79 | 458 ± 92 |
| No. of fibroids | 2.1 ± 0.4 | 2.1 ± 0.4 | 1.9 ± 0.5 |
| Main volume of fibroids (cm ³) | 62.8 ± 27.7 [†] | 41.5 ± 24.2 | 58.5 ± 31.0 |
| Echogenicity of main fibroid | 5.1 ± 1.3 [†] | 3.4 ± 0.9 | 4.8 ± 1.5 |
| Resistance index | | | |
| Uterine artery | 0.66 ± 0.07 [†] | 0.79 ± 0.08 | 0.63 ± 0.08 |
| Main fibroid | 0.53 ± 0.08 [†] | 0.77 ± 0.06 | 0.55 ± 0.07 |

Values are presented as mean ± SD. There were no significant differences between groups at T0 for all parameters.

*T1, group A, versus T0, group B, *p* < 0.01.

†T0, group A, versus T1, *p* < 0.001.

Table III. Main outcome measures

| | Group A (n = 35) | | Group B (n = 32) | |
|---|---------------------------|---------------------------|---------------------------|--------------------------|
| Global operative time (min, mean ± SD) | 98.5 ± 26.1* | | 113.3 ± 35.1* | |
| Blood loss (ml, mean ± SD) | 171.8 ± 70.9 [†] | | 232.1 ± 68.1 [†] | |
| Red blood cell count (×10 ⁶ /ml) | 4.6 ± 0.3 [‡] | 4.3 ± 0.5 [§] | 4.4 ± 0.4 [‡] | 3.9 ± 0.6 [§] |
| Hemoglobin (gm/dl) | 13.1 ± 0.8 [‡] | 12.2 ± 1.1 [§] | 12.7 ± 1.0 [‡] | 11.4 ± 1.3 [§] |
| Serum iron (µg/dl) | 62.6 ± 14.2 [‡] | 57.1 ± 12.8N [§] | 60.7 ± 13.9 [‡] | 53.4 ± 12.3 [§] |

Change in T0 to Tf, group A versus group B, *p* < 0.05.

*Group A versus group B, *p* < 0.05.

†Group A versus group B, *p* < 0.01.

‡T0 versus Tf, *p* < 0.05.

§Tf, group A, versus Tf, group B, *p* < 0.05.

Table IV. Operative time as function of ultrasonographic predictors

| | Operative time (min) | |
|------------------------------|---|-----------------------|
| | Group A | Group B |
| No. of fibroids | | |
| <3 | 91.4 ± 24.0 (n = 24) | 99.9 ± 32.7 (n = 21) |
| >3 | 114.1 ± 24.5 (n = 11) | 139.0 ± 24.4 (n = 11) |
| | * [91.4 ± 24.0 (n = 24) ————— * ————— 139.0 ± 24.4 (n = 11)] [†] | |
| Volume of main fibroid | | |
| <60 ml | 89.7 ± 22.3 (n = 20) | 96.5 ± 29.6 (n = 20) |
| >60 ml | 110.4 ± 26.8 (n = 15) | 141.3 ± 24.6 (n = 12) |
| | * [89.7 ± 22.3 (n = 20) ————— † ————— 141.3 ± 24.6 (n = 12)] [‡] | |
| Echogenicity of main fibroid | | |
| <3 | 128.3 ± 17.6 (n = 9) | 114.9 ± 8.1 (n = 10) |
| >3 | 88.2 ± 20.0 (n = 26) | 112.6 ± 42.4 (n = 22) |
| | ‡ [128.3 ± 17.6 (n = 9) ————— * ————— 112.6 ± 42.4 (n = 22)] [‡] | |

Values in parentheses are numbers of patients. Operative time in minutes.

**p* < 0.05.

†*p* < 0.01.

‡*p* < 0.001.

omectomy and subsequent uterine wall reconstruction. The preoperative administration of GnRH analog resulted in significantly lower blood loss at surgery, lower operative time, and significantly higher red blood cell count and hemoglobin and iron levels postoperatively.

In regard to concerns related to the ultrasonographic predictors, as expected, when the number of fibroids was more than two and the volume of the main fibroid was

>60 cm³, we had a significant improvement in the operative time after the preoperative 2-month course of GnRH analog. Doppler velocimetry of the uterine vessels and the major vessels of the main fibroid²⁴ did not show any correlation with the efficacy of the GnRH analog preoperative treatment in reducing the operative time.

Inversely, when we consider those fibroids with an echogenicity score <3, the pretreated group had a significantly longer operative time (*p* < 0.05). Considering the

predominant relevance of the traction maneuvers in laparoscopic myomectomy, the difficulty in adequately grasping the tumor is the key element in the longer operative time. The softening of the fibroid tissue is probably related to degenerative changes induced by the GnRH analog pretreatment,¹⁰ particularly in those fibroids without an adequate fibrous "skeleton" and thus with the appearance as hypoechoic at the admission ultrasonography. From a pathologic point of view, these fibroids, when pretreated, showed a predominance of areas of coagulative necrosis and mixoid degeneration. Furthermore, the pretreated patients with hypoechoic main fibroids had a longer surgery time than the rest of the pretreated patients and the untreated patients with hypoechoic myomas, showing unequivocally the negative effect of preoperative GnRH analog treatment for these kinds of uterine fibroids.

These data clearly show how the efficacy of a 2-month course of GnRH analog in reducing blood loss before laparoscopic myomectomy requiring wall reconstruction is well documented in our study. Furthermore, our data show the effectiveness of pretreatment related to the operative time in fibroids ≥ 60 cm³, in multiple fibroids, and, comprehensively, in all cases except hypoechoic fibroids. In these fibroids preoperative GnRH analog treatment further lowers the density of the tumor, thereby causing the enucleation of the fibroid from the uterine walls to be much more cumbersome.^{22, 25}

In conclusion, from our prospective randomized comparative study we can suggest the use of GnRH analog pretreatment before laparoscopic myomectomy requiring wall reconstruction in all cases except markedly hypoechoic fibroids.

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