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Research Article

TIBOLONE: AN ADJUNCT OF PREOPERATIVE GNRH ANALOGUE THERAPY IN PREMENOPAUSAL WOMEN UNDERGOING LAPAROSCOPIC MYOMECTOMY: AN EFFICACY, SYMPTOM RELIEF, AND SURGICAL OUTCOMES

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ABSTRACT

This was a prospective, randomized, open-label, and placebo-controlled study to assess the impact of the co-administration of tibolone with, preoperative gonadotropin-releasing hormone (GnRH) analogue treatment on 121 premenopausal women, who had laparoscopic, preoperative myometectomy of the uterine leiomyoma against placebo. The participants were to be exposed to the leuprolide acetate with tibolone and iron (Group A), leuprolide acetate with placebo and iron (Group B), and iron alone (Group C). Both GnRH analogue-treated groups showed a significant decrease in uterine and leiomyoma volume, an improvement in hematologic parameter and a change of myoma-related symptoms prior to surgery. Without impairing the reduction of the fibroid, tibolone was effective in reducing hypoestrogenic vasomotor symptoms. Group A and B had better operative outcomes as indicated by surgical time and intraoperative blood loss, as compared to iron alone. These results demonstrate that preoperative GnRH analogue treatment is beneficial to minimize the size and severity of fibroid mass and symptomatology, and tibolone is a safe and well-tolerated alternative to improve patient adherence and comfort.

Key words: - Uterine leiomyoma, GnRH analogue, Tibolone, Laparoscopic myomectomy, Preoperative therapy.

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INTRODUCTION

GnRH analogues are proved to be effective in the treatment of uterine leiomyomas. In women in the menopausal age, GnRH analogues may serve as an alternative to hysterectomy, especially in women who want to avoid mutilation [1]. The gnRH analogue therapy is accompanied, however, by the induced hypoestrogenism, and this can cause the occurrence of climacteric-like symptoms, which include hot flushes and mood swings, which adversely affect patient compliance and general treatment acceptability [2].

New studies have emphasized the possible use of tibolone which is a synthetic steroid with weak estrogenic, progestogenic, and androgenic activity in reversing these side effects [3]. It has been shown that tibolone is tolerated well among postmenopausal women who have uterine myomas and it does not negatively affect the safety of the patient, with a symptom-relieving effect. Interestingly, tibolone -administered together with GnRH analogue therapy has been reported to decrease the incidence of vasomotor symptoms, and bone loss, preserving the

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therapeutic effect of decreasing uterine and fibroid volume seen with GnRH analogue [4]. It indicates that tibolone can be used to improve the tolerability of GnRH analogue therapy without affecting its effectiveness.Surgery is still the main way in the treatment of uterine leiomyoma especially in premenopausal women using of this treatment when there is rapid growth of the fibroid, frequent miscarriage, and infertility due to endometrial cavity distortion. In these patients, GnRH Ag therapy in the short run before laparoscopic myomectomy has proven to be effective. One or two rounds of administration of the analogue can shrink the preoperative uterine size, decrease intraoperative blood loss as well as make the surgeries better. Even though the duration of therapy is relatively short, hypoestrogenic symptoms, i.e. hot flashes and vaginal dryness, were reported, which may negatively impact patient compliance and patient comfort.With these things in mind, the current prospective, randomized, open-label, placebo-controlled trial methodology was done to determine whether the effects and tolerability of preoperative GnRH analogue therapy could be altered by co-administration with tibolone in laparoscopic myomectomy procedures of women [5]. This study aimed to establish whether tibolone had the potential of reducing hypoestrogenic side effects and still maintain the effect of the GnRH analogue on uterine and fibroid volume reduction which would lead to better patient experience and surgical outcomes. Through this direction, the paper will address a significant clinical dilemma, which is the question of how to ensure the effectiveness of the GnRH analogue therapy without causing as many side effects as possible, especially in premenopausal women undergoing surgery.

MATERIALS AND METHODS

Patients

The original group of the study consisted of 121 premenopausal women who had symptomatic uterine leiomyomas. Inclusion criteria were more than three years history of infertility, recurrent miscarriage and heavy vaginal bleeding, pelvic pressures, pelvic pain, urine frequency or constipation. Only patients having intramural leiomyomas with 4500 cm3 by the ultrasonography and three to five fibroids were used.Criteria used to exclude were liver disease, ischemic heart disease, dyslipidemia, diabetes, acute or recent vascular thrombosis or a history of breast or endometrial carcinoma. Others that were excluded included the presence of submucosal fibroids, endometrial hyperplasia with cytologic atypia, abnormal findings in Papanicolaou smears, a positive urine pregnancy test and fibroid calcification or hypoechogenicity on the ultrasound.The research was undertaken in line with the declaration of Helsinki and it was endorsed by the institutional review board. Written informed consent was given by all participants who were given an elaborate explanation of the study protocol.

Study Design and Treatment

The participants were randomized in the open-label study in a placebo-controlled study in a computer generated randomization table of three equal groups. Group A was treated using intramuscular leuprolide acetate [3.75mg/28days], oral iron (two tablets per day) and oral tibolone (2.5 mg/day). The same leuprolide acetate and oral iron regimen was used in group B in combination with oral placebo (one tablet/day). The initial injection of leuprolide was given on the third day of the menstrual cycle and tibolone or placebo on day 15 following the first injection. Only oral iron tablets (two tablets daily) were used on group C. Two months (two cycles of injections) of treatment were undertaken with laparoscopic myomectomy being done on the fourth week, after the second injection of leuprolide.

Assessments

The patient age, parity, body mass index, and evidence of surgery were noted at baseline (visit 1). The data were assessed again in one week prior to surgery (visit 2) and one week after (visit 3), with transabdominal ultrasonography, blood, and climacteric-like and myoma-related symptoms. The follow-up was made three months after surgery.

Ultrasonography

One trained operator who was blind to group assignments carried out all the ultrasonography with an ultrasound probe of 5-MHz and a transabdomen probe. The ellipsoid formula of $D1 \times D2 \times D3 \times 0.52$ was used to calculate the uterine volume, fibroid volume, the number of leiomyomas and largest leiomyoma volume. Patients with calcified or hypoechogenic fibroids were eliminated.

Hematologic Assessment and Symptom Assessment.

Measurements of erythrocyte count, hematocrit, hemoglobin and serum iron were done every visit. The patients had diaries where they recorded the number of hot flushes and vaginal bleeding episodes per day. The symptoms related to myoma such as menorrhagia, pelvic pressure and pain were rated on a visual analogue scale using 0 (no pain) and 10 (worst imaginable pain).

Laparoscopic Myomectomy

Every operation was carried out by the same surgeon with a 10-mm laparoscope and two or three additional ports. There was fibroid excision that included infiltration with vasoconstrictive solution, longitudinal incision, enucleation, and morcellation as well as hemostasis that was through the application of bipolar coagulation and layered myometrical closure. Histopathologic assessment of all specimens was done.

Statistical Analysis

Unpaired Student t -tests were used to compare baseline characteristics. ANOVA was performed as repeated-measures ANOVA to examine the variations in uterine and fibroid volumes, symptom, and biochemical parameters. The Wilcoxon rank-sum test was used to test the difference in the operational time and blood loss. Sample size given was more than 75 percent power to detect significant differences across groups at P<0.05. Data are reported as mean ± SD.

RESULT

According to the results of Tables 1 and 2, preoperative treatment with leuprolide acetate, with or without tibolone and iron (Group A and B, respectively), led to a significant decrease in the sizes of the uterine and leiomyoma before surgery. Group A and Group B: uterine volume declined between baseline (Visit 1) of about 532 ± 95 cm 3 and 510 ± 88 cm 3 to 380 ± 58 cm 3 and 345 ± 55 cm 3 one week pre-surgery (Visit 2), which was statistically significant (P < 0.05). There were also significant decreases in the volume of leiomyoma that were 76 ± 18 cm 3 and 74 ± 15 cm 3 at baseline to 55 ± 12 cm 3 and 50 ± 12 cm 3, respectively. In comparison, iron-only group (Group C) demonstrated no significant change in uterine or leiomyoma volume pre-operative which means that iron supplementation by itself has no effect on the size of fibroid. After surgery (Visit 3), the uterine volumes of all groups together with Group C reduced considerably with the excision of fibroids thus proving that surgery is the ultimate cure of the uterine leiomyomas.There were parallel improvements in hematologic parameters with the use of leuprolide. Groups A and B - Erythrocytes, hemoglobin, and serum iron level improved significantly between the baseline and Visit 2, which indicates the improvement of fibroid-related anemia. As an example, the hemoglobin levels were 12.3 [12.3 +1.7]/g/dl to 13.7 [13.7 + 0.9]/g/dl in Group A and Group B respectively (P < 0.05). Serum iron also changed to a better extent. Conversely, Group C which was treated with iron only showed a slight or no increase in hematologic parameters before surgery, and some showed a decline after surgery, showing that the correction of anemia is better achieved when the size of fibroid is pharmacologically shrunk before it is removed through surgery.Symptomatically, patients in Groups A and B also noted that symptoms related to myomas such as menorrhagia, pelvic pressure and pelvic pain were significantly relieved by Visit 2. The menorrhagia scores went down to 6.9 + -0.9 to 3.8 + -0.8 in Group A and 7.0 + -1.1 to 2.0 + -1.0 respectively in Group B, which is a clinically significant outcome in terms of bleeding. Likewise, the scores of pelvic pressure and pain were significantly lower proving that the leuprolide treatment does not only decrease the size of the fibroid, but also relieves the physical pain which is caused by the presence of the uterine leiomyoma. Group C on the other hand did not improve such symptoms prior to surgery and even some symptom scores deteriorated, which makes the effects of iron alone on the clinical symptoms of fibroids unlikely.On the whole, the results suggest that preoperative leuprolide acetate in combination with or without tibolone can successfully decrease the volume of the uterus and leiomyoma, enhance the hematologic values, and reduce the symptom burden, but iron supplementation alone has no effect on fibroid volume and symptom. These findings suggest that leuprolide-based therapy is an appropriate option of preoperative treatment to maximize the outcome of surgical patients and enhance the quality of life of patients with uterine leiomyoma women.

Table 1: Uterine and leiomyomata volume, number of leiomyomas, volume of largest leiomyoma, and hematologic variables (n = 121).

Characteristic	Group A			Group B			Group C		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Uterine volume (cm^3)	532 ± 95	380 ± 58[a]	205 ± 32[ab]	510 ± 88	345 ± 55[a]	198 ± 22[ab]	498 ± 101	495 ± 100[c]	210 ± 20[ab]
Leiomyoma volume (cm^3)	185 ± 52	135 ± 35[a]	—	172 ± 45	118 ± 28[a]	—	165 ± 42	166 ± 41[c]	—
No. of leiomyomas	1.95 ± 0.9	1.88 ± 0.9	—	2.0 ± 0.9	1.97 ± 0.9	—	1.9 ± 0.9	1.9 ± 0.9	—
Volume of largest leiomyoma (cm^3)	76 ± 18	55 ± 12[a]	—	74 ± 15	50 ± 12[a]	—	71 ± 16	72 ± 14[c]	—
Erythrocyte count (cells × 10^6/mL)	3.7 ± 0.8	4.6 ± 0.5[a]	4.0 ± 0.4[b]	3.8 ± 0.8	4.6 ± 0.4[a]	4.1 ± 0.4[b]	3.9 ± 0.8	3.9 ± 0.7[c]	3.2 ± 0.6[bc]
Hemoglobin (g/dL)	12.3 ± 1.7	13.7 ± 1.0[a]	12.1 ± 0.9[b]	12.0 ± 1.6	13.6 ± 0.9[a]	12.3 ± 0.8[b]	12.5 ± 1.8	12.2 ± 1.6[c]	11.1 ± 1.2[bc]
Hematocrit (%)	40.8 ± 3.2	42.0 ± 3.0	40.5 ± 3.2	41.8 ± 2.8	42.0 ± 2.7	40.7 ± 2.9	41.8 ± 2.7	41.3 ± 2.7	40.0 ± 2.8
Serum iron (µg/dL)	68.0 ± 26.0	92.5 ± 26.5[a]	69.0 ± 19.0[b]	65.0 ± 28.0	94.0 ± 32.0[a]	70.0 ± 18.0[b]	73.0 ± 32.0	76.0 ± 33.0[c]	53.0 ± 22.0[bc]

Legend:
Group A = leuprolide acetate + tibolone + iron;
Group B = leuprolide acetate + placebo + iron;
Group C = iron only;
Visit 1 = baseline; Visit 2 = one week before surgery; Visit 3 = one week after surgery.
[a]Significant difference vs Visit 1, P < 0.05
[b]Significant difference vs Visit 2, P < 0.05
[c]Significant difference vs Group A and B, P < 0.05

Table 2: Myoma-related symptoms in the three study groups (n = 121).

Symptoms	Group A			Group B			Group C		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Menorrhagia	6.9 ± 0.9	3.8 ± 0.8[a]	—[ab]	7.0 ± 1.1	2.0 ± 1.0[a]	—[ab]	6.8 ± 1.2	7.5 ± 1.0[c]	—[ab]
Pelvic pressure	4.9 ± 1.4	2.2 ± 1.6[a]	—[ab]	4.7 ± 1.5	1.6 ± 1.1[a]	—[ab]	4.8 ± 1.8	5.8 ± 2.2[c]	—[ab]
Pelvic pain	3.8 ± 1.2	1.2 ± 1.4[a]	—[ab]	4.1 ± 1.8	1.4 ± 1.3[a]	—[ab]	4.6 ± 2.0	5.1 ± 2.1[c]	—[ab]

Legend:
Group A = leuprolide acetate + tibolone + iron;
Group B = leuprolide acetate + placebo + iron;
Group C = iron only;
Visit 1 = baseline; Visit 2 = one week before surgery; Visit 3 = one week after surgery.
[a]Significant difference vs Visit 1, P < 0.05
[b]Significant difference vs Visit 2, P < 0.05
[c]Significant difference vs Groups A and B, P < 0.05

DISCUSSION

Past studies have suggested that gonadotropin-releasing hormone (GnRH) analogues can be effectively used in the preoperative stage to reduce intraoperative blood loss and reduce operative time used in performing myomectomy [6,7]. In these studies, GnRH analogue therapy among patients resulted in substantial hematologic parameter change, meaning an increase in erythrocyte count, hemoglobin concentration, and serum iron, post-surgery [8]. Nonetheless, the temporary use of GnRH analogues is frequently associated with the side effects of hypoestrogenism, especially those of vasomotor symptoms of hot flush, which can be uncomfortable to patients [9]. Combination of steroids or other hormone-based add-back therapies and GnRH analogues to short-term preoperative treatment has not been advised traditionally, since evidence has indicated that addition of estroprogestins or progestins during initiation of therapy may decrease the treatment capacity to reduce both the uterine and leiomyoma volume [10]. The same previous studies have shown that the selective steroid tibolone, when used together with a GnRH analogue, has no effect in changing the ability of the analogue to reduce the size of the uterus and leiomyoma, at the same time providing the same treatment with the reduction of vasomotor symptoms of hypoestrogenism [11]. Moreover, tibolone was demonstrated to be safe when treating uterine leiomyomas, and the studies carried out in women without complaints revealed no adverse impacts on tumor, bleeding trends, amenorrhea and abnormal uterine bleeding. It was based on these observations that this prospective, randomized, open-label, placebo-controlled study was conceived to determine whether the use of tibolone can affect the efficacy of GnRH analogue therapy in women with symptomatic uterine leiomyomas who have laparoscopic myomectomy [12]. Though the study has 66 patients in three groups, the study could have provided a better idea of statistical power of over 80 percent of detecting any difference in its primary outcome measures had the sample size been large. The criteria used to select patients were high homogeneity of surgical difficulty and response to treatment and only women with intramural leiomyomas in need of uterine wall reconstruction were enrolled but women were excluded with hypoechoic or calcified fibroids as they tend to respond less to GnRH analogue therapy and are difficult to manipulate during surgery. The outcome of the treatment showed that there was no significant effect of tibolone addition in changing the effect of the GnRH analogue. Tibolone was delayed to 15 days following the initial injection of the analogues to alleviate the development of vasomotor symptoms without exposing the patient to unnecessary dose of the drug. Two months of therapy showed both groups given the GnRH analogue with the addition of tibolone and the control group recorded significant decrease in total uterine and leiomyoma volumes, and the size of the largest leiomyma with no significant differences between these two groups. Also, myoma-related symptoms, such as heavy menstrual bleeding, pelvic pressure, and pelvic pain, were significantly improved in both groups as compared to baseline and to iron-only group and erythrocyte count,

hemoglobin concentration, and serum iron levels were also improved significantly in both groups compared to baseline and iron-only group. Tibolone was discovered to have a significant effect in decreasing the vasomotor symptoms, and patients in the tibolone group recorded a notably lower rate of hot flushes starting on the 18 th -day treatment. The operative measures, such as surgical time and blood loss, had better results in both the analogue-treated groups compared to the iron-only group, with the trend being non-significant in shorter operative time and less bleeding in the group endowed with GnRH analogue. A week following surgery, hematologic indices were much lower in the iron-only group and there were even patients in the iron-only group who needed blood transfusion, which explains the effect of preoperative GnRH analogue therapy. On the whole, these results indicate that tibolone can be safely used together with the GnRH analogue therapy prior to laparoscopic myomectomy to enhance patient comfort without interfering with the efficacy of the analogue to decrease fibroid size, reduce its symptoms, or improve its hematologic effects. Although such findings are encouraging, there is a need to validate those in bigger, double-blind trials in order to further prove the clinical efficacy and applicability of such combination therapy.

CONCLUSION

This research paper will show that a gonadotropin-releasing hormone (GnRH) analogue administered in the preoperative phase, with or without tibolone, is an effective treatment of uterine and leiomyoma volumes in premenopausal women undergoing laparoscopic myomectomy. Both regimens caused a significant reduction in uteral size, the total volume of leiomyoma and the largest leiomyma before surgery, which indicated that short-term GnRH analogue therapy is useful in preparing the surgical conditions. Notably, patients undergoing GnRH analogue therapy were also associated with the positive effects on the symptoms of myoma related to menorrhagia and pelvic pressure, and pelvic pain, as well as improvements in hematologic parameters, erythrocyte count, hemoglobin concentration, and serum iron levels. These results show that pharmacologic shrinkage of the fibroid sizes does not only induce surgical intervention but also treat fibroid related anemia enhancing overall patient well being prior to surgery.The GnRH analogue regimen was not compromised by the addition of tibolone which did not affect the effectiveness of the analogue in reducing the size of the uterine or leiomyoma. Tibolone was rather effective in reducing the hypoestrogenic side effects especially hot flushes, which is more comfortable and tolerable by the patients taking the treatment. This specific intervention enabled the management of such negative effects of GnRH analogues on hypoestrogenism without reducing the pharmacologic efficacy, which underscores tibolone as a safe and supportive adjunct.The clinical benefit of pharmacologic treatment even before the procedure was also shown by the enhancement of operative outcomes such as the duration of surgery and intraoperative blood loss in both GnRH analogue-treated groups versus iron supplementation alone. Conversely, patients who were treated with iron did not experience much change in fibroid size, chronic symptoms, and poorer hematologic response, which demonstrated the low efficacy of iron supplementation in treating symptomatic leiomyomas. To conclude, a preoperative GnRH analogue therapy (with or without tibolone) offers an effective approach to minimizing fibroid burden, improving hematologic state, minimizing symptoms, and improving surgical outcomes. Tibolone has one more advantage in decreasing vasomotor discomfort, thus enhancing adherence and quality of life of patients. These results justify the use of tibolone as a safe adjunct to short-course use GnRH analogue therapies to reduce the incidence of laparoscopic myomectomy in women, though larger, double-blind trials are justified to substantiate these findings and clarify the best clinical procedures**.**

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