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Original Research Article

TAMING FIBROID-RELATED BLEEDING: ORMELOXIFENE OR COMBINED HORMONAL CONTRACEPTIVES – WHICH WORKS BEST?

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ABSTRACT

Background: Uterine fibroids are a leading cause of hysterectomy worldwide. An efficacious and cost-effective medical treatment option may reduce hysterectomy-associated morbidity. The present study was undertaken to evaluate the efficacy of ormeloxifene in the medical management of AUB-L and compare it with combined hormonal contraceptives (CHC).

Materials and Methods: It was a Prospective comparative study. A total of 76 women in the age group 35-45 years, having abnormal uterine bleeding due to leiomyoma (PBAC score >100) were included, and randomized into two groups. Women in one group were given Ormeloxifene 60 mg twice weekly for 6 months and in another group combined hormonal contraceptives containing ethinyl estradiol 30 µg with levonorgestrel 150 µg for 21 days starting from day 1 or 2 of the cycle, were given for 6 months. Participants were followed after 3months, 6 months and then at 9 months, that is 3 months after completion of treatment. Primary outcome measure was change in PBAC Score. Other outcomes noted were change in hemoglobin concentration, change in leiomyoma size and volume, changes in dysmenorrheal VAS score and satisfaction with treatment.

Results: There was statistically significant decrease in PBAC score in both the groups at each follow-up visit, however the improvement was significantly more in ormeloxifene group (p value <0.05). The decrease in mean PBAC scores was 80.63 % in group 1 at 6 months and 63.45% in group 2. Similar observation was made in mean hemoglobin concentration. However, there was no statistically significant change in leiomyoma volume in either of the group at 6 months and at 9 months. prolonged cycles was the most common side-effect seen with ormeloxifene.

Conclusion: Ormeloxifene is a non-steroidal, non-hormonal drug and an effective, safe and acceptable option for medical management of heavy menstrual bleeding associated with leiomyoma uterus.

Keywords: Ormelexifene; Combined hormonal contraceptives (CHCs); Leiomyoma; Abnormal uterine bleeding.

INTRODUCTION

Uterine leiomyoma is the most common benign gynecological tumor, affecting about 20% - 50% of women in the reproductive age group.[1] Following their genesis, uterine leiomyomas are estrogen and progesterone-sensitive tumors. Consequently, they develop during the reproductive years, and conditions with sustained estrogen exposure encourage leiomyoma formation.

About 50% of the women with uterine leiomyoma remain asymptomatic.[2] Of the ones who are symptomatic, the symptoms highly depend on the location of uterine leiomyoma. Sub-mucosal uterine fibroids are more likely to be symptomatic than sub-serosal fibroids, especially in relation to menstrual disorders. Other symptoms include lower abdominal pain, dysmenorrhea, infertility, pressure effects such as feeling of heaviness in pelvis, increased urinary frequency and urgency.

Although there has been progress in understanding the molecular changes in leiomyomas and the surrounding myometrium and endometrium, the reason for the wide range of clinical symptoms remains unclear. Compared with standard surgical treatments, medical therapy avoids possible surgery-related complications. In addition to this, medical management can have several objectives like reducing the size of fibroids, avoiding surgery in symptomatic women near menopause, providing a nonsurgical treatment to women who desire to preserve their uterus, extending preoperative time to stabilize a serious or co-morbid medical condition, improving the hematologic status of women who are anemic before surgery.

The treatment options can be non-hormonal or hormonal. Non-hormonal methods include use of non-steroidal anti-inflammatory drugs and tranexamic acid, an anti-fibrinolytic.

Hormonal methods include progesterone containing preparations in oral, injectable or implantable form, combined hormonal agents, gonadotropin releasing hormone (GnRH) analogs, and certain novel drugs such as anti-progestins (eg. Mifepristone), selective progesterone receptor modulators (eg. Ulipristal acetate), selective estrogen receptor modulator (eg. Ormeloxifene).

Combined hormonal contraceptives (CHCs) primarily act by inhibiting ovulation through negative feedback to the hypothalamus and pituitary gland, resulting in decreased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and in decreased ovarian production of sex steroids (estrogen and progesterone).

Ormeloxifene is a selective estrogen progesterone receptor modulator (SERM). SERMs are the drugs that selectively bind to estrogen receptors and act as estrogen agonists in some tissues and estrogen antagonists in others. Ormeloxifene antagonizes the effect of estrogen on uterine and breast tissue and stimulates its effect on vagina, bone, cardiovascular and central nervous system. Ormeloxifene significantly reduces endometrial thickness, and this is one of the reasons for reduced blood loss.[3]

An effective and cost-effective medical treatment option may reduce hysterectomy-associated morbidity. Although the efficacy of ormeloxifene is established in AUB-E and AUB-O, there is limited literature on its efficacy in AUB-L.

Hence, the present study is undertaken to evaluate the efficacy of ormeloxifene in the medical management of AUB-L and compare it with combined hormonal contraceptives (CHC), one of the commonly prescribed medical treatments for AUB.

MATERIALS AND METHODS

This is a hospital-based prospective comparative study conducted in the Department of Obstetrics and Gynaecology over a period of 1.5 years. Ethical clearance for the study was obtained from the institutional ethics committee. The inclusion criteria for the study were women aged 35-45 years, experiencing abnormal uterine bleeding due to leiomyoma. Heavy menstrual bleeding was documented using the pictorial blood loss assessment chart (PBAC), and women with a PBAC score greater than 100 were included.

Exclusion criteria included women with unexplained vaginal bleeding, uterine size greater than 12 weeks, submucosal leiomyomas type 0 or 1, atypia on endometrial histopathology, concurrent ovarian pathology or adnexal disease, hemoglobin levels less than 7 gm%, or those who were hemodynamically unstable. Additional exclusion criteria were arterial and thromboembolic diseases, premalignant or malignant gynecological or breast diseases, liver disease, systemic illnesses causing menorrhagia, or any prior or concurrent hormonal treatment. Women seeking surgical management, those desiring pregnancy or currently pregnant, and lactating women were also excluded from the study.

Methodology

Seventy-six women of reproductive age, who presented to the outpatient department with complaints of heavy menstrual bleeding and met the inclusion criteria, were enrolled in the study after obtaining written informed consent. They were randomly divided into two equal study groups: Group A, which received ormeloxifene, and Group B, which received combined hormonal contraceptives. A detailed medical history, along with a complete general physical, systemic, and gynecological examination, was conducted. Investigations, including complete blood counts and ultrasound, were performed.

Group A patients were given ormeloxifene 60 mg twice a week for 6 months, while Group B received combined hormonal contraceptives containing ethinyl estradiol 30 µg and levonorgestrel 150 µg for 21 days, starting from day 1 or 2 of the menstrual cycle, for a period of 6 months.

Participants were followed up at 3 months, 6 months, and again at 9 months (3 months after completing treatment). At each visit, the number of bleeding days, cycle length, PBAC score, and any side effects were recorded. Hemoglobin levels and ultrasound were repeated after 6 and 9 months. The dysmenorrhea VAS (Visual Analog Scale) score was also noted at the end of the study. No hormones or other agents to control abnormal uterine bleeding (AUB) were prescribed during the study period.

The primary outcome measure was the change in PBAC score. Other outcomes included changes in hemoglobin concentration, leiomyoma size and volume, dysmenorrhea VAS score, patient satisfaction with treatment, and reasons for discontinuation (such as bleeding patterns, side effects, etc.

RESULTS

In our study, a total of 76 cases with AUB-L were enrolled and randomly divided into two groups. Group A included patients who received ormeloxifene 60 mg twice a week, while Group B received combined hormonal contraceptives containing ethinyl estradiol 30 µg and levonorgestrel 150 µg for 21 days in a cycle, over a period of 6 months. In Group A, one woman underwent a hysterectomy during the course of the study, while the remaining patients continued the treatment for 6 months. In Group B, two women discontinued treatment. A total of 37 patients in Group A and 36 patients in Group B were followed up at 6 and 9 months, respectively.

Both study groups were similar in demographic profile, including age, parity and BMI. The mean age in Group A was 38.76 ± 2.93 years, while in Group B it was 37.95 ± 2.37 years. The mean parity in Group A was 2.5, and in Group B it was 2.28 (Table 1).

Heavy menstrual bleeding (PBAC score greater than 100) was present in all cases. In Group A, 12 women (31.58%) had frequent cycles (cycle length <21 days), while 10 women (26.32%) had frequent cycles in Group B. Along with heavy menstrual bleeding, dysmenorrhea was present in 11 women (28.95%) in Group A and in 13 women (34.21%) in Group B (Figure 1).

The majority of leiomyomas in both groups were of type 4, intra-mural type. There was a significant reduction in objective blood loss during the study period, as assessed by the pictorial blood loss assessment chart, in both groups.

The decrease in PBAC score was found to be significant starting from the third month of treatment. In Group A, the PBAC score decreased from a baseline value of 320 ± 71.93 to 60.68 ± 42.75 at 6 months and 72.79 ± 42.94 at 9 months (3 months after treatment). In Group B, a statistically significant reduction in blood loss was observed starting from the third month after initiating treatment (from 300.67 ± 54.27 at baseline to 118 ± 74.85 at 6 months and 124.13 ± 75.48 at 9 months). This decrease in PBAC score was progressive and significant at the end of 6 months in both groups (p value <0.0001). While there was an increase in the PBAC score at 9 months compared to 6 months, it remained significantly lower than the baseline (p value <0.0001). The decrease in PBAC score was more pronounced in Group A compared to Group B at all follow-up points: 250.34 vs 182.47 at 3 months, 260.18 vs 188.05 at 6 months, and 248.08 vs 176.34 at 9 months. The difference was statistically significant at all follow-ups (Table 2). In terms of percentage, the decrease in mean PBAC scores was 80.63% in Group A at 6 months and 63.45% in Group B. The decrease in PBAC score in Group A was statistically significant at all time points (3 months, 6 months, and 9 months).

The mean hemoglobin concentration increased from 9.27 ± 0.82 gm/dl at baseline to 11.11 ± 0.865 gm/dl at 6 months and 11.41 ± 0.74 gm/dl at 9 months in Group A. In Group B, the mean hemoglobin concentration increased from 9.47 ± 0.71 gm/dl at baseline to 10.81 ± 0.79 gm/dl at 6 months and 11.2 ± 0.67 gm/dl at 9 months. Although hemoglobin levels increased in both groups, the increment was greater in the ormeloxifene group (20.22% vs 14.34% at 6 months and 23.56% vs 18.72% at 9 months). This difference was statistically significant ($p < 0.05$). (Table-3)

There was no statistically significant change in the volume of leiomyomas in either group at 6 months or 9 months (p value > 0.05). However, there was a statistically significant improvement in dysmenorrhea (decrease in VAS score) in both groups at 6 months.

No major side effects were experienced by women in either group. In Group A, the most common side effect was prolonged cycles, reported by 18.42% (n=7) of women. Prolonged cycles were observed in 7.89% (n=3) of women in Group B. The most common side effect in Group B was gastrointestinal symptoms, including nausea and dyspepsia, observed in 15.78% (n=6) of women. These symptoms were seen in 7.89% (n=3) of women in Group A. Other side effects included abnormal vaginal discharge, seen in 10.52% (n=4) of women in Group B and 2.6% (n=1) in Group A. Ovarian cysts were observed in 10.5% (n=4) of women in Group A. None of the subjects experienced intrauterine or ectopic pregnancies during the study. (Figure 2)

In Group A, 25 out of 38 women and in Group B, 20 out of 38 women were very satisfied with the treatment. During the study period, one woman in Group A did not experience any relief in symptoms at the first follow-up visit (3 months) and opted for surgical management. In Group B, two women discontinued treatment after 3 months, citing excessive nausea and vomiting, as well as no relief in symptoms, as the reasons. The overall satisfaction rate was higher in Group A due to the easier dosage schedule, which led to better patient compliance. However, the difference was not statistically significant (p value > 0.05).

Table 1: Demograpic profile of patients

Parameter		Group A	Group B	p- value
Age	35-40 years	28 (73.68%)	32 (84.21%)	0.256
	41-45 years	10 (26.38%)	6 (15.79%)	
	Mean age	38.76	37.95	
Parity	P1	3 (7.9%)	6 (15.8%)	0.845
	P2	17 (44.7%)	18 (47.4%)	
	P3	14 (36.8%)	12 (31.6%)	
	≥P4	4 (10.5%)	2 (5.2%)	

	Mean parity	2.5 ± 0.80	2.28 ± 0.79	
BMI(kg/m^2)	20-25	10 (26.3%)	10 (26.3%)	0.84
	25-30	20 (52.6%)	22 (57.89%)	
	30-35	8 (21.1%)	6 (15.79%)	
	Mean BMI	26.85 ± 2.84	26.73 ± 2.66	

Table 2: PBAC score

PBAC score	Group A	Group B	P value
Pretreatment	320 ± 71.93	300.67 ± 54.27	<0.0001
6 month	60.68 ± 42.75	118 ± 74.85	
9 month	72.79 ± 42.94	124.13 ± 75.48	

Table 3: Comparison of mean haemoglobin in group A and group B

Haemoglobin	Group A	Group B	P value
Pretreatment	9.27 ± 0.82 gm/dl	9.47 ± 0.71 gm/dl	<0.05
6 month	11.11 ± 0.865 gm/dl	10.81 ±0.79 gm/dl	
9 month	11.41 ± 0.74 gm/dl	11.2 ± 0.67 gm/dl	

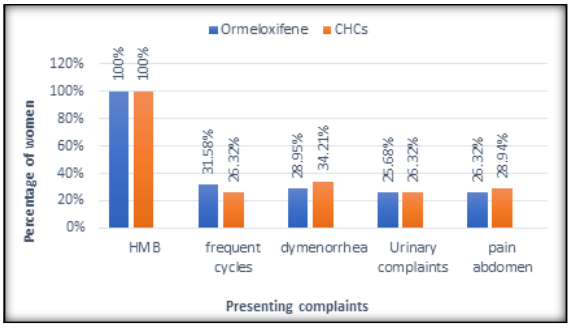

Figure 1: Presenting complaints of women in group A and group B

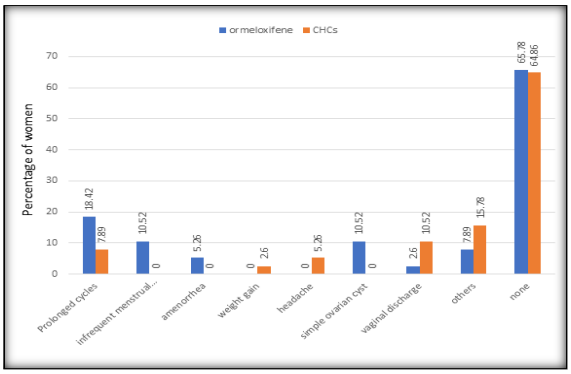

Figure 2: Comparison of side effects in group A & group B

DISCUSSION

Combined hormonal contraceptives and ormeloxifene have been used in women with dysfunctional uterine bleeding. As currently, there is lack of literature comparing these two medical methods of management of abnormal uterine bleeding due to leiomyoma, this study was undertaken to study comparative efficacy and acceptability of these two drugs in Indian women.

The incidence of leiomyoma increases with age; 4.3 per thousand women-years for the age group 25 to 29 years and 22.5 per thousand women-years for the age group 40 to 44 years.[4]

Hence in the current study, women included were of the age group 35 to 45 years.

In the present study, objective assessment of menstrual blood loss was done using a semiquantitative method: a pictorial blood loss assessment chart. Although quantitative methods are available for eluting hemoglobin from sanitary products, this approach is cumbersome and might have deferred participation in the study.[4]

As observed in the present study, there was a significant decrease in blood loss, measured by reduction in PBAC score during the study period after using ormeloxifene for 6 months. Similar results were obtained by Dasgupta et al, where PBAC score changed from 184.41±84.97 to 83.77±55.46 at 6 months in women with AUB-L, a reduction of 54.57%.5 Kriplani et al observed reduction of 68.1% and 77.4% in PBAC score with therapy, at the second and fourth months respectively.[6]

Similar to ormeloxifene, there was a statistically significant reduction in menstrual blood loss starting from the third month after initiating treatment with CHCs. Orsini et al also noted a significant reduction of more than two days of menstrual flow with the use of COCs for 24 months.[7] Similarly, an RCT by Sayed et al, in 2010, comparing COCs with LNG-IUS for the treatment of fibroids, using the alkaline hematin method, the reduction of menstrual blood loss was 13.4% ± 11.1% with the use of COCs over 12 months, while the reduction in PBAC score was 53.5% ± 51.2%.[8]

In our study, reduction in PBAC score was more with ormeloxifene at all follow-up visits as compared to CHCs (p value<0.0001). Similar observation was made by Kriplani et al. in women with AUB-L, and Chhatrala et al. in women with DUB.[9,10] In a study conducted by Khare et al., decrease in mean PBAC score was 41.7% with ormeloxifene and 18% with oral contraceptive pills in women with DUB.[11]

In the present study, there was an overall statistically non-significant change in leiomyoma volume after use of oremloxifene for 6 months (p value > 0.05). Similar findings were observed by Dasgupta et al. who explained these findings on the basis of the different response and activity of the two Estrogen Receptors (ER) in the uterus, i.e. ERα (predominantly present in endometrium) and ERβ (in ovarian

follicles). Hence, Ormeloxifene may be a good option to give symptomatic relief to the women with AUB-L, but may not decrease the leiomyoma size.[5]

In the present study, dysmenorrhea was present in 11 women (28.94%) in group A and 13 women (34.2%) in group B. The subjective assessment of dysmenorrhea was done using VAS scale, which is an analogue scale for pain quantification. Statistically significant decrease in Vas score, hence significant improvement in dysmenorrhea was produced by both ormeloxifene and CHCs (p value <0.05). Also, both the groups were comparable in reducing the VAS score (p value=0.512).

In group A i.e. ormeloxifene group, the most common side effect was prolonged cycles, seen in 18.42% [n=7] women. Although amenorrhea is beneficial to health in women with heavy menstrual bleeding, it can also lead to discontinuation of the method in a significant number of women especially in younger age group as a result of anxiety and cultural non-acceptance. But it was not a reason for discontinuation of treatment in present study because of age group of patients and proper pre-treatment counselling.

Most of the women taking ormeloxifene and CHCs were very satisfied with the treatment, 25 out of 38 in group A (65.79%) and 20 out of 38 in group B (52.63%). Ormeloxifene dosage schedule, marked relief in symptoms and minimal side-effects and hence is more acceptable and desirable to women with AUB-L.

CONCLUSION

Ormeloxifene, a non-steroidal and non-hormonal medication, is an effective, safe, and well-tolerated option for managing heavy menstrual bleeding associated with uterine leiomyomas. It offers a convenient and cost-effective alternative to surgical and other invasive procedures for women with AUB-L. However, further research involving larger sample sizes is required to better evaluate its efficacy and safety in the management of AUB-L.

Limitation(s)

The present study is a single-centre study with less number of subjects which is a limitation of this study. More randomised and larger multicentric trials are needed to compare these drugs for better results.

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