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RESEARCH ARTICLE

Evaluation of the Role of Ormeloxifene in Abnormal Uterine Bleeding

[1]Ritu Sharma, [2]Savita R Singhal

ABSTRACT

Aim: This is a prospective study to find the effect of ormeloxifene on menstrual blood loss and its side effects in patients with abnormal uterine bleeding (AUB).

Materials and methods: Fifty women in the age group of 30 to 52 years with AUB were enrolled in the study. After baseline assessment, each patient was given 60 mg of ormeloxifene orally twice a week for first 3 months, then once a week for the next 3 months. The patients were followed up after 1, 3, and 6 months. The effect of ormeloxifene was evaluated by a change in the pictorial blood loss assessment chart (PBAC) score, passage of clots during menstruation, hemoglobin level, endometrial thickness (ET), and dysmenorrhea. Side effects of the drug were also noted at each visit; p-value < 0.05 was taken as significant.

Results: There was statistically significant reduction in median PBAC score from baseline 360 to 113, 73, and 41.5 after 1, 3, and 6 months. There was significant reduction in ET, passage of clots, and dysmenorrhea at each visit. Mean hemoglobin level increased significantly by 1.56 gm% after 6 months treatment. Adverse effects included amenorrhea (28%), ovarian cyst (11.3%), nausea (4.5%), headache (2%), and weight gain (4.5%). There was no major side effect requiring termination of treatment.

Conclusion: Ormeloxifene is a safe and efficacious alternative for medical therapy in the management of AUB.

Clinical significance: Ormeloxifene can be used in women with AUB to avoid the side effects of hormonal treatment and unnecessary hysterectomies.

Keywords: Abnormal uterine bleeding, Amenorrhea, Ormeloxifene, Pictorial blood loss assessment chart score.

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[1]Senior Resident, [2]Senior Professor and Head

[1]Department of Obstetrics and Gynecology, W Pratiksha Hospital, Gurugram, Haryana, India

[2]Department of Obstetrics and Gynecology, Pt. Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak Haryana, India

Corresponding Author: Ritu Sharma, Senior Resident Department of Obstetrics and Gynecology, W Pratiksha Hospital Gurugram, Haryana, India, Phone: +918685089060, e-mail: ritus581@gmail.com

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INTRODUCTION

Abnormal uterine bleeding is a commonly encountered gynecological problem accounting for 19.1% visits to the physician and 25% of gynecological surgeries.[1] This is diagnosed when there is a substantial change in frequency, duration, or amount of bleeding during or between periods.[2] Menorrhagia is defined as blood loss of more than 80 mL per cycle or PBAC score more than 100.[3,4] The AUB affects women in all the age groups, occurring more commonly just prior to menopause. It has a great impact on physical, social, emotional, and economical aspects of a woman's life in the current era. The AUB should be managed by a stepwise approach with the goal of use of medical therapeutic modalities followed by the least surgical modalities.[5] Medical management has the potential to reduce the number of surgical interventions and ultimately the cost burden on the patient. Both hormonal and nonhormonal pharmacological agents can be used, but the associated side effects and contraindications have led to increased demand of nonhormonal drugs as compared with hormonal drugs.

Ormeloxifene is a newer nonhormonal, nonsteroidal selective estrogen receptor modulator, which is currently used in medical management of patients with excessive bleeding. In India, it was introduced over 20 years ago as the first nonsteroidal contraceptive agent, but later on, its beneficial effects in menorrhagia, osteoporosis, and benign breast disease were observed. It has estrogen antagonistic action on breast and uterine tissue and agonistic effect on skeletal tissue.[6] It has a wide therapeutic index and is safe during lactation.[7] It has a simple dosage schedule of 60 mg twice a week for 3 months, followed by 60 mg once a week for use in medical management of AUB. In perimenopausal women, it provides added benefits of protection against breast cancer and osteoporosis. It has good acceptability and compliance due to its low cost, minimal side effects, and simple dosage schedule. So, the present prospective trial was conducted to study the effect of ormeloxifene on menstrual blood loss in patients of AUB and to observe its side effects.

MATERIALS AND METHODS

This prospective clinical trial was conducted in the Department of Obstetrics and Gynaecoloogy, Pt. Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, India, from March 2013 to September 2014, after approval from the ethical committee. Fifty women in the age group of 30 to 52 years with AUB were recruited for the study after informed consent. The women with coagulation disorders, using contraceptive (oral and intrauterine device),polycystic ovarian disease, pregnancy, uterine fibroid more than 10 weeks, submucous fibroid, polyp, suspected genital/breast malignancy, atypical endometrium, and postmenopausal bleeding were excluded from the study. At enrollment, after taking detailed menstrual history including number of bleeding days, amount of blood loss, cycle length, and dysmenorrhea, gynecological examination followed by assessments of complete hemogram, bleeding time, clotting time, and thyroid-stimulating hormone were done. Ultrasonography was performed to see any structural pathology and measure ET. Endometrial sampling was performed in women aged more than 35 years. Objective assessment of amount of blood loss was done by calculating PBAC score, which was obtained by assigning a score of 1, 5, and 20 to superficially, moderately, or fully soaked sanitary pad respectively, and a score of 1 and 5 for passage of small- and large-sized clots respectively (Fig. 1). Score of more than 100 was taken as excessive bleeding.

The patients were given 60 mg ormeloxifene orally twice a week for 3 months and then once a week for the next 3 months and they were instructed to use the same type of sanitary pads. Then, patients were followed up at 1, 3, and 6 months and at each visit; PBAC scoring, cycle length, dysmenorrhea, hemoglobin level, and side effects of the drug were assessed. Endometrial thickness was repeated at 3 and 6 months. Patients were taken as failure if menorrhagia was not controlled after 3 months of the treatment. In the study, primary outcome measure was decreased as in menstrual blood loss according to PBAC scoring and secondary outcome measures were improved as in hemoglobin, ET, and dysmenorrhea.

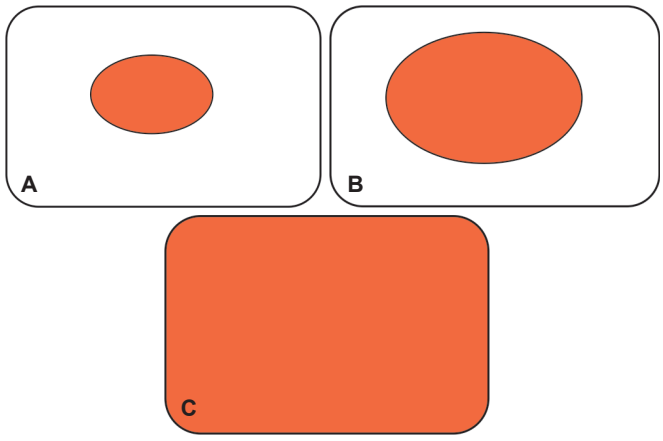

Fig. 1: PBAC scoring to assess menstrual blood loss

Statistical analysis was performed using paired t test, unpaired t test, and chi squared test. Percentages were calculated for categorical data and mean ± standard deviation (SD) or median with range for continuous variable data. A p-value < 0.05 was considered as significant.

RESULTS

Fifty women with AUB were enrolled, and out of these 50, in six women the treatment was discontinued after 3 months due to no response; hence, only 44 women completed the 6-month treatment (Flow Chart 1). The age of patients ranged from 32 to 50 years and mean age was 39.3 ± 4.9 years. Most of the women were educated (84%) and from a urban background (52%). 98% of the women were multiparous and mean parity was 2.78 ± 1.1. 42% women had fibroid uterus and 10% had endometrial hyperplasia. The results are shown in Tables 1 to 3.

At the end of study, 70% (21/44) of women achieved PBAC score less than 100. Fourteen patients (28%) had amenorrhea after start of treatment and majority of these patients (71.4%) were more than 39 years. Cycle length was analyzed in 30 patients after excluding the patients

Flow Chart 1: Outcome of the patients enrolled in the study

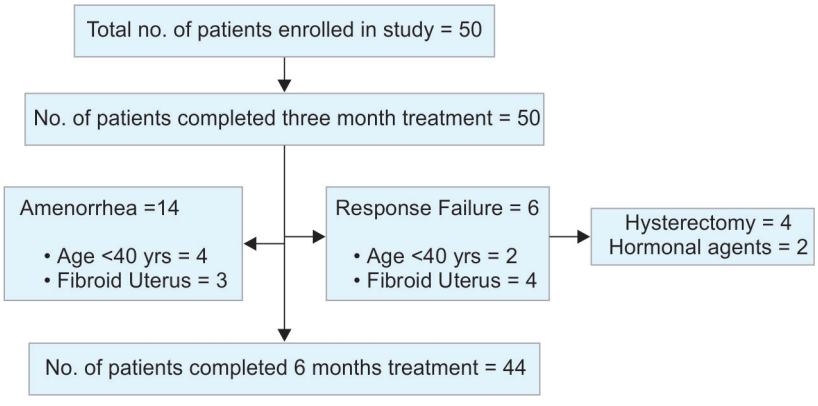

Table 1: Patient distribution according to PBAC scoring

PBAC score	*At enrollment (n)*	*At 1 month (n)*	*At 3 months (n)*	*At 6 months (n)*
Up to 100	0	11	16	21
101–300	20	19	12	7
301–500	13	3	4	2
501–700	12	0	1	0
701–900	3	3	2	0
901–1000	2	0	1	0
Amenorrhea (0 score)	–	14	14	14
Total no of patients	50	50	50	44
Median (IQR)	360 (251–558)	113 (0–218)	73 (0–180)	41.5 (0–89.25)
% reduction	–	68.61	79.72	88.47
p-value	–	0	0	0

n = Number of patients; IQR: Interquartile range

Table 2: Various parameters at 1, 3, and 6 months of treatment

Parameter	*At enrollment (mean ± SD)*	*After 1 month, mean ± SD (p-value)*	*After 3 months, mean ± SD (p-value)*	*After 6 months, mean ± SD (p-value)*
Duration of bleeding (days)	7.38 ± 3.6	3.44 ± 3.4 (0.005)	3.36 ± 3.44 (0.001)	2.45 ± 2.2 (0.029)
Passage of clots (no of patients)	46/50	18/50 (0.001)	7/50 (0.001)	7/50 (0.001)
Cycle length duration (days)	26.4 ± 6.6	30.2 ± 9.5 (0.087)	34.6 ± 16.9 (0.011)	43.3 ± 21.6 (0.000)
Dysmenorrhea (no of patients)	33/50	16/50 (0.000)	6/50 (0.000)	2/50 (0.000)
ET (mm)	8.9 ± 3.1	–	8.38 ± 2.4 (0.048)	7.82 ± 2.3 (0.034)
Hemoglobin level (gm%)	9.00 ± 1.3	9.22 ± 1.2 (0.001)	9.73 ± 1.4 (0.000)	10.56 ± 1.1 (0.000)

Table 3: Side effects of ormeloxifene

Side effects	*1 month, n (%)*	*3 months, n (%)*	*6 months, n (%)*
Nausea	12 (24%)	5 (10%)	2 (4.5%)
Weight gain	0	1 (2%)	2 (4.5%)
Headache	1 (2%)	1 (2%)	0
Ovarian cyst	–	4 (8%)	5 (11.3%)
Amenorrhea	–	14 (28%)	14 (28%)
No of patients	50	50	44

n = No of patients

who had treatment failure (6 patients) or had amenorrhea (14 patients). The mean increase in hemoglobin was 1.56 gm% and mean reduction in ET was 1.08 mm at the end of 6 months. The percentage reductions in number of patients with passage of clots during menstruation after 3- and 6-month treatments were 73.9 and 84.8% respectively, and 93.9% patients had improvement in dysmenorrhea at 6 months.

DISCUSSION

Hormonal therapy, which is the mainstay of medical management of AUB, is associated with steroidal side effects and unscheduled breakthrough bleeding. This problem raises the requirement for research in the field of nonhormonal and nonsteroidal options for the medical management of AUB. Ormeloxifene is a nonsteroidal, nonhormonal, and selective estrogen receptor modulator drug, which is very effective in controlling menstrual blood loss. The effect of ormeloxifene is attributed to its anti-estrogenic effect on endometrium and breast tissue and estrogenic effect on bones. In perimenopausal women, it provides added benefits of protection against breast cancer and osteoporosis. It has good acceptability and compliance due to its low cost, minimal side effects, and simple dosage schedule.

In the present study, with the use of ormeloxifene at a dose of 60 mg twice a week, PBAC scores showed 68.6, 79.7, and 88.47% reductions after 1, 3, and 6 months of therapy (Table 1). This reduction was evident in the very first cycle, which is advantageous, as most of women want quick response and compliance was good. Agarwal and Singh[8] found 90.42% reduction in median PBAC score after 6 months of ormeloxifene treatment in dysfunctional uterine bleeding patients, which is comparable to the present study. There was significant reduction in mean duration of bleeding at each visit. Kriplani et al[9] also found significant decrease in number of bleeding days during menses.

Excessive blood loss during menstruation causes anemia in patients with AUB. The results of the present study showed 1.56 gm% increase in mean hemoglobin level (p-value 0.000, Table 2). After 6 months of the treatment, the majority of the women, 77.2% (34/44), had hemoglobin more than 10 as compared with 24% (12/50) at enrollment. Komaram et al[10] also found significant increase of 1.3 gm% in hemoglobin, which is comparable to the present study. The ormeloxifene

use was associated with significant decrease of 1.08 mm in ET after 6 months, which is a beneficial effect as reduction in ET is a definite objective evidence showing decrease in blood loss. Significant reduction in ET was also reported by Chandra et al.[11]

Passage of clots during menses depicts excessive flow. The present study showed 73.9 and 84.8% reduction in number of women with passage of clots after 3 and 6 months respectively. Similar results were also found by Chandra et al.[11] Most of the women had advantage of relief from dysmenorrhea along with decrease in blood loss.

Ovarian cyst (11.3%) and amenorrhea (28%) were the main observed side effects of ormeloxifene. There was spontaneous regression in next cycle in most of the cysts. Amenorrhea was mostly observed in perimenopausal women and it was well accepted by most of them.

CONCLUSION

Ormeloxifene, a nonhormonal drug, causes reduction in menstrual blood loss, improvement in hemoglobin and dysmenorrhea, and has no major side effects. It is cost effective and has a simple dosage schedule. Thus, ormeloxifene is a suitable alternative for medical therapy in the management of AUB. The study was limited by sample size. Larger randomized multicentric trials with long-term follow-up are needed to validate the efficacy and safety of this drug.

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