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CONTEMPORARY PERSPECTIVE STUDY

Ormeloxifene *versus* Medroxyprogesterone Acetate (MPA) in the Treatment of Dysfunctional Uterine Bleeding: A Double-Blind Randomized Controlled Trial

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ABSTRACT

Objective: To find the effectiveness of ormeloxifene *vs* medroxyprogesterone acetate (MPA) to reduce blood loss in dysfunctional uterine bleeding (DUB).

Materials and methods:

Design—A double blind randomized controlled trial.

Data source—The women attending gynecology OPD in teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum, India for menorrhagia, meeting the selection criteria were enrolled into the study.

Randomization—Computer-generated randomization, with block size of two, was done into two groups.

Intervention—One group (group A) received capsule ormeloxifene 60 mg to be taken two days a week at an interval of 3 days, and a placebo form of medroxyprogesterone acetate for 21 days starting from day 2 to 5 of the menstrual cycle for three consecutive cycles. Other group (group B) received medroxyprogesterone acetate (MPA) 10 mg for 21 days starting from day 2 to 5 of the menstrual cycle, and a placebo form of ormeloxifene for 2 days a week with an interval of 3 days for three consecutive cycles. The drug and its placebo were in similar capsular form. All the participants were ensured to use the similar type of sanitary napkins, and transvaginal ultrasonography was done to note the endometrial thickness (ET) before and after the drug therapy.

Blinding—The department of clinical pharmacy prepared the drug packets and kept the randomization code till the data was analyzed, thus ensuring the double blinding.

Outcome: Participants were interviewed during subsequent cycle. Pictorial blood assessment chart (PBAC) score was used to calculate blood loss during menses at the first and subsequent three months.

Data analysis: The mean PBAC scores and endometrial thickness were compared in two groups.

Results: The mean pretreatment PBAC scores in group A and group B were 262.26 and 238.71 ml respectively. The mean PBAC scores at the end of the study period were 73 and 108 in group A and B respectively, reporting an overall reduction in mean blood loss by 85.7 and 54.76% ($p = 0.0205$) in group A and B respectively. Thus, there was a significant reduction in blood loss in the group receiving ormeloxifene. The reduction in the mean endometrial thickness was more in ormeloxifene group. However, this was not statistically significant ($p = 0.0942$).

Conclusion: Ormeloxifene is more effective as compared to MPA in reducing the blood loss in the treatment of DUB.

Keywords: Ormeloxifene, Progesterone, Medroxyprogesterone acetate (MPA), Dysfunctional uterine bleeding.

INTRODUCTION

Menstrual disorders are the second most common gynecological conditions resulting in hospital referrals. Approximately, 20 to 30% of women, in the age group of 35 to 50 years, seek to medical help for heavy menstrual bleeding.[1] In today's world, where women represent a major sector of paid force in both the developing and developed countries, any regular source of debility like menorrhagia has important economic and personal consequences. It results in iron deficiency anemia affecting their physical, social, emotional and/or material quality of life.[2] Surgical therapy appears more promising but is associated with other personal, social and economic consequences.

Therefore, medical therapy is a principle tenet of treatment. Evidence states that progestins form the gold standard and are ineffective in the treatment of ovulatory type of DUB.[3]

Thus, there is a need for an ideal therapy to encompass both types of DUB creating a hypoestrogenic environment without disturbing other estrogenic positive effects. Selective estrogen receptor modulators (SERMs) have been identified to occupy a place in between estrogens and antiestrogens. These

compounds have estrogenic activities, which are tissue selective. Ormeloxifene is an optimally designed SERM, which behaves like an estrogen antagonist in uterus with mild agonistic action on vagina, bone and serum lipids.[4-6]

Ormeloxifene has been evaluated for the management of menorrhagia but not against progesterone. This study was an attempt to find out the effectiveness of ormeloxifene against medroxyprogesterone acetate (MPA).

MATERIALS AND METHODS

A prospective double-blind randomized control trial was carried out at teaching hospital attached to JN Medical College, Belgaum, Karnataka, India. Women attending gynecology OPD in the age group of 35 to 50 years for menorrhagia meeting and selection criteria were recruited after informed consent. After clinical examination, they were subjected to hemoglobin estimation, transvaginal sonography, visual inspection of cervix with acetic acid (VIA) and colposcopy. Those with pelvic pathology, systemic disorders, severe anemia, chronic cervicitis and cervical dysplasia were excluded. Recruitment period was for ten months (September 2008-June 2009).

The protocol was approved by the institutional review board of the hospital. Enrolled participants were randomized into two groups. Group A received capsule ormeloxifene 60 mg twice weekly with an interval of 3 days and placebo form of capsule, Medroxyprogesterone acetate for a period of 21 days starting from day 2 to 5 of the cycle for three consecutive cycles. Group B received capsule, medroxyprogesterone acetate 10 mg for a period of 21 days and placebo form of ormeloxifene twice weekly with a minimum interval of three days starting from day 2 to 5 of the cycle for three consecutive cycles. The placebos were certified to be clinically inert. The drug and its placebo form were available in similar capsular form, so as to match in both groups.

Plastic pouches with medication for 3 months were prepared for each participant of both groups. These were then numbered as per the randomization plan by the department of clinical pharmacy. Numbered pouches were returned to the investigator and given to the women in sequential order, with a follow-up at monthly interval for 3 months.

All women were instructed to use sanitary napkin of similar kind, not containing absorbent gel. Participants were taught to fill the pictorial blood assessment chart (PBAC) at every monthly cycle. In this study, menorrhagia was defined as PBAC score of >100. Two pretreatment baseline cycles were compared to three consecutive treatment cycles.

Women with continuous vaginal bleeding for more than 10 days were started with the medication on the day of visit itself.

At the end of 3 months of study period, mean PBAC score was calculated. TVS was repeated for endometrial thickness (ET) in proliferative phase—day 8 to 12 of cycle. Decoding the randomization plan was done by the department of clinical pharmacy after the data analysis.

Sample Size

The sample size of 84 with 42 in each group was determined on the basis of an ability to have a reduction of blood loss by 75%, calculated on basis of previously conducted studies. Taking the power of the test as 80% with an error and dropout rate of 10% each, effective sample size was calculated.

Data Analysis

The mean and SD were calculated for pictorial blood assessment chart (PBAC) score and endometrial thickness. The periodic mean PBAC in two groups were compared using unpaired 't-test'. The mean endometrial thickness in two groups were compared using unpaired 't' test.

The number of cases with PBAC score ≤ 100 were counted and the test of two sample proportions were applied to find the significant difference in the efficacy between the two drugs. The difference between the two groups of $p < 0.05$ was defined as statistically significant.

RESULTS

Around 350 women with menorrhagia were screened, 120 were eligible and 96 women consented to participate. Only 84 women, who completed the 3 months follow-up, were included in the analysis with 42 in each group. The two groups were matched in age and parity, 59.24% of women in group A and 54.76% in group B had received previous treatment for which they had failed to respond or symptoms had recurred.

Mean PBAC score in group A before treatment was 262.26 range (160-380) and the mean PBAC score in group B before treatment was 238.71 range (130-410). Majority of them had score above 200 in both the groups (Table 1). They were comparable.

At the end of one month of treatment, mean PBAC scores were 141.74 and 141.54 in group A and B respectively, i.e. it had reduced by 46 and 40.7% in group A and B respectively. The efficacy of treatment was comparable in two groups and there was no statistically significant difference in reduction between two groups.

At the end of two months, PBAC score had reduced by 77.02 and 55.03% from the baseline in group A and B respectively. There was a significant reduction in group A ($p = 0.016$).

At the end of third month, PBAC score had reduced by 87.83 and 60% from the baseline in group A and B respectively. There was a significant reduction in group A compared to group B ($p = 0.014$) (Table 2).

The mean PBAC scores at the end of the study period were 73 and 108 in group A and B, reporting an overall reduction in mean blood loss by 85.71 and 54.76% in group A and B respectively. Thus, there was a significant reduction in menstrual blood loss in group receiving ormeloxifene against the group receiving medroxyprogesterone acetate ($p = 0.0205$) (Table 3).

Table 1 PBAC score before treatment

PBAC	*Group A*	*Group B*
100-200	5	14
200-300	21	20
> 300	16	8
Total	42	42

Table 2 Monthly PBAC score after treatment

PBAC	*After 1 month*		*After 2 months*		*After 3 months*	
	Group A	*Group B*	*Group A*	*Group B*	*Group A*	*Group B*
< 100	16	7	35	14	35	16
100-185	15	27	1	19	1	18
> 185	10	5	1	3	1	1
Total	41	39	37	36	37	35

Table 3 Mean PBAC score after treatment

Mean PBAC	*Group A*	*Group B*
< 100	29	11
100-185	7	22
> 185	1	2
Total	37	35

Table 4 Endometrial thickness before treatment

Endometrial thickness	*Group A*	*Group B*
0-5	6	5
5-10	21	28
10-15	15	9
Total	42	42

Table 5 Endometrial thickness after treatment

Endometrial thickness	*Group A*	*Group B*
0-5	19	6
5-10	17	27
10-15	1	2
Total	37	35

The mean endometrial thickness before the treatment in group A was 7.81 and in group B was 6.08. The two values were comparable (Table 4).

Mean endometrial thickness in group A was found to be 4.94 mm and in group B was found to be 5.86 mm. There was a reduction in endometrial thickness in group receiving ormeloxifene compared to the group receiving medroxyprogesterone acetate ($p = 0.0942$), however this was statistically not significant (Table 5). It was observed that the effectiveness for ormeloxifene was more as compared to MPA group in the reduction of menorrhagia (87.71% *vs* 54.76%). The failure to respond to the treatment was significantly less in ormiloxifene group as compared to MPA (11.9% *vs* 35.71%, $p = 0.042$).

The predominant side effect noted with ormeloxifene was amenorrhea and observed in 9.5% of women.

DISCUSSION

The DUB should be viewed as a part of the general endocrine disturbance affecting the entire system of women and not as a mere local pathology of the uterus or reproductive organ.[7,8] The approach to management is to ensure general well-being and improve quality of life in addition to control the bleeding.

Medical management and avoidance of surgery is always recommended, as the short period of drug therapy bridges the temporary phase of menstrual alterations successfully, wherein young subjects settle down with normal cycles and elderly subjects attain menopause.[9,10]

Preference should be for nonsteroidal agents, as steroidal agents will only aggravate the existing endocrine dysfunction. Ormeloxifene, a nonsteroidal drug, is easier to administer, cost effective, and has lesser side effects.[11-13] The mean PBAC scores at the end of the study period were 73.7 and 108 in group A and B respectively. The overall reduction in mean blood loss was 85.71 and 54.76% in the two groups respectively. Ormeloxifene was more effective in the treatment of DUB as compared to cyclical progesterone.

A study conducted in the year 2000 on 70 subjects using ormeloxifene in a dosage of 30 mg twice weekly for 6 months reported a reduction in menorrhagia by 80 to 87.78%.[12]

A similar study was conducted on 42 women with menorrhagia administering tablet. Ormeloxifene 60 mg twice weekly for 3 months and then once a week for one month showed reduction in menorrhagia by 99.7% at 4 months.[14]

The results of the present study were comparable with other studies.

Reduction in endometrial thickness is a definitely objective evidence showing reduction in mean blood loss. In the present study, though there was a reduction in ET in the ormeloxifene group, this was not statistically significant may be because of shorter course of treatment compared to other studies. A similar study using ormeloxifene in DUB showed significant reduction in ET after 6 months of treatment.[4] It was observed that 80% of subjects, who failed to respond to ormeloxifene, had ET < 5 mm. Though, in theory ormeloxifene is supposed to improve mean blood loss even in hypoestrogenic states by virtue of exerting a mild estrogenic effect by means of agonistic action of ER-b receptors, such an effect has not been seen in the present study.

The main strength of the present study is that it is a double-blind randomized trial and in the present trial, the PBAC score of Higham et al was used as it has better sensitivity and predictive value as compared to the PBAC score of Jassen et al.[15,16]

Small sample size and single center trial may be limitations of this study. A multicenter larger randomized controlled trial is recommended to confirm the observations of this trial.

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