

EFFICACY OF ORMELOXIFENE IN MANAGEMENT OF DYSFUNCTIONAL UTERINE BLEEDING

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ABSTRACT

Objective: The objective was to evaluate the efficacy of ormeloxifene in dysfunctional uterine bleeding (DUB) with respect to bleeding pattern and improvement in hemoglobin (Hb).

Methods: This was an interventional study on 99 patients of DUB visiting the gynecology outpatient department over 1 year using semi-structured pro forma. After voluntary participation of patients, tablet ormeloxifene was given at the dose of 30 mg biweekly for 2 months. In case of a therapeutic response as informed by the patient, the dose was reduced to 30 mg weekly for a further period of 4 months. All patients were treated for 6 months. Type, amount, and duration of bleeding, frequency of menstrual cycle, passage of clots, and impact on Hb were assessed.

Result and Observations: Menorrhagia was the main type of bleeding. 36–40 years of age group was the most common. After the intervention, 76.8% of women achieved a duration of bleeding of 4–5 days, and in 87% of women, menstrual cycle became regular. Passage of clots was reduced by 71.83%. Mean Hb concentration of study participants increased by 0.5 g/dl at the end of the study.

Conclusion: Ormeloxifene is effective alternative and appears to be a promising option for the medical management of DUB.

Keywords: Dysfunctional uterine bleeding, Ormeloxifene, Hemoglobin, Menorrhagia, Selective estrogen receptor modulators.

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INTRODUCTION

Dysfunctional uterine bleeding (DUB) is abnormal genital tract bleeding based in the uterus and found in the absence of demonstrable structural or organic pathology [1,2].

Such bleeding is often the result of endocrinological dysfunction and is associated with the absence of ovulation in 80–85% of cases [3,4]. DUB is a common debilitating problem among women in all age groups and accounts for 20% of gynecology clinic visits [5]. Even though a number of treatment modalities are available, a reliable drug for the management of DUB should meet the requirements such as drug should be effective, convenient to take, cost of the drug must be low, with minimal side effects, and the drug should have longest safety margin. The latest of the pharmacological agents that have become available for the treatment of DUB are selective estrogen receptor modulators. These are designer drugs which have an affinity to the estrogen receptor and act like estrogens in some tissues and have antiestrogenic effects in others [6]. Ormeloxifene is a non-steroidal selective estrogen receptor modifier with strong antiestrogen and weak estrogenic and antiprogesterin properties [7]. Ormeloxifene not only preferred as oral contraceptive but also useful for the management of DUB and advanced breast cancer [8-10].

METHODS

This was an interventional study of 99 patients, carried out in gynecological outpatient department of medical college and hospital at Dhule district. It was 1 year study and comprised of semi-structured type pro forma including information related to the physical status of participants. Patients' weight was noted, and menstrual history was taken in detail. Patients who were between 20 and 40 years of age, who are not desirous of pregnancy, and who were with no organic disease

were included. A total of 106 patients registered in the OPD of the gynecology department were the study population.

Emphasis was paid on the type of bleeding, duration of bleeding, type of blood loss, duration of cycles, passage of clots, and effect on hemoglobin concentration. Treatment taken for present complaints was enquired and previous menstrual history was also noted. History suggestive of bleeding disorders, diabetes, and thyroid dysfunction was also taken. Obstetric and family history was noted.

Of these patients, 99 patients who were fulfilling inclusion criteria's and who were ready to participate in the study voluntarily were enrolled. Voluntarily participated patients were given tablet ormeloxifene at the dose of 30 mg biweekly for 2 months. The patient was reassessed after the first 2 months. Blood loss was assessed in a subjective manner and by hemoglobin estimation. In case of a therapeutic response as informed by the patient, the dose was reduced to 30 mg weekly for a further period of 4 months. All patients were treated for 6 months. Patients were analyzed after 6 months, and data collected were tabulated and analyzed using computer technology by the SPSS package of statistics. Protocol was submitted to the Institutional Ethics Committee, and the study was started after approval.

RESULTS AND OBSERVATIONS

Of 99 patients, nearly 50.51% of women were in 36–40 years of age group. Maximum number of women, i.e., 52.53% were of third parity. Menorrhagia was the main type of bleeding (58.2%) (Table 1).

In age-wise distribution, 53.40% of women who were having menorrhagia were in 36–40 years of age group (Table 2).

Duration of bleeding was 4–5 days in 12.1%, but after ormeloxifene, it changed to 76.8% (p=0.001) (Table 3).

Table 1: Age, parity, and bleeding pattern-wise distribution of patients

S. No	Parameter	Number of patients (%)
1	Age (Years)	
	20-25	9 (9.1)
	26-30	14 (14.1)
	31-35	26 (26.3)
	36-40	50 (50.5)
2	Parity	
	0	4 (4.04)
	1	9 (9.09)
	2	17 (17.17)
	3	52 (52.52)
	4	17 (17.17)
3	Type of bleeding	
	Menorrhagia	58 (58.2)
	Metropathia hemorrhagica	10 (10)
	Polymenorrhagia	23 (24)
	Metrorrhagia	8 (7.8)

Table 2: Age group wise distribution of type of bleeding

Parameters	Age in years (%)				Total
	20-25	26-30	31-35	36-40	
Menorrhagia	5 (8.6)	8 (13.8)	14 (24.1)	31 (53.4)	58 (100)
Polymenorrhagia	4 (17.4)	2 (8.7)	7 (30.4)	10 (43.5)	23 (100)
Metropathia hemorrhagica	0 (0)	2 (20)	3 (30)	5 (50)	10 (100)
Metrorrhagia	0 (0)	2 (25)	2 (25)	4 (50)	8 (100)
Total	9 (9.1)	1 (14.1)	26 (26.3)	50 (50.5)	99 (100)

Table 3: Effect of ormeloxifene treatment for 6 months on the duration of menstrual bleeding

Duration of bleeding	Pre-intervention n (%)	After intervention n (%)	p value
<4 days	0 (0)	21 (21.2)	0.001
4-5 days	12 (12.1)	76 (76.8)	0.001
6-7 days	42 (42.4)	0 (0)	0.001
≥8 days	45 (45.5)	2 (2)	0.001

After intervention for 6 months, the frequency of menstrual cycle which was irregular in 74.7% changed to regular (12.1%), and regular cycle pattern (25.3%) increased to 87.9% (Table 4).

Amount of bleeding returns to normal in 68.7% and heavy blood loss turned to 0% from 85.9% (Table 5).

Women showing the history of passage of clots were significantly decreased from 78.9% to 7.07%.

At the time of participation in the study, it was observed that all women were having hemoglobin below 12 g/dl. The cumulative percentage of 70.7% of women was having hemoglobin <10 g/dl, of which 32.3% of women had hemoglobin concentration between 9 and 10 g/dl. After the intervention, the cumulative percentage of women having hemoglobin <10 g/dl reduced to 61.6%, of which most of them, i.e., 36.4% were having hemoglobin (Hb) from 9 to 10gm/dl. Furthermore, there was a significant improvement in Hb concentration in women having Hb in between 10 and 12 g/dl from 29.3% to 38.4% after intervention. Mean Hb concentration of study participants increased from 9.5 g/dl to 10 g/dl at the end of the study.

DISCUSSION

Wide varieties of treatment modalities are available for treating DUB, from medical therapy to minimally invasive surgery in the form of

Table 4: Effect of 6 months ormeloxifene on the frequency of menstrual cycle

Frequency of menstrual cycle	Pre-intervention n (%)	After intervention n (%)
Irregular	74 (74.7)	12 (12.1)
Regular	25 (25.3)	87 (87.9)

Chi-square (McNemar) p=0.001

Table 5: Effect of 6 months of ormeloxifene on amount of bleeding

Amount of bleeding	Pretreatment n (%)	After treatment n (%)
Normal	0 (0)	68 (68.7)
Moderate	14 (14.1)	31 (31.3)
Heavy	85 (85.9)	0 (0)

Wilcoxon sign rank test p=0.001

Table 6: Comparison among related studies

Studies	Improvement in mean Hb (g/dl)	% reduction in passage of clots
Current study	0.5	71.83
Grover <i>et al.</i> [14]	0.42	66.66
Mandal <i>et al.</i> [11]	0.72	80.6
Bhattacharyya and Banerji [19]	2.53	91.18
Singh <i>et al.</i> [18]	1.89	51.7
Jacob <i>et al.</i> [20]	1.39	93.3
Agarwal and Singh [13]	0.7	67
Ahmed <i>et al.</i> [21]	1.96	68
Godha <i>et al.</i> [16]	1.2	87
Komaram <i>et al.</i> [15]	1.3	59
Dhananjay <i>et al.</i> [22]	2.26	-
Khan <i>et al.</i> [23]	1.3	-

transcervical resection of the endometrium, thermal ablation, and others to conventional hysterectomy. However, medical treatment should be the preferred modality of treatment when possible [11]. A medical management is the first line of therapy for dysfunctional uterine bleeding. The agents that have been used to treat menorrhagia include iron, cyclooxygenase inhibitors, desmopressin, antifibrinolytics, gonadotropin-releasing hormone agonists, androgens, combined oral contraceptives, and progestins [12]. Ormeloxifene has been found to be safer and effective alternative in the treatment of DUB.

The most common age presentation in our study was between 31 and 40 years. It was believed earlier that DUB is more common in extremes of reproductive ages, but the current scenario does not show strictness in above fact [2]. Study by Agarwal and Singh selected age range of 20-50 years [13]. In clinical practice, age can vary from 30 to 45 years. DUB was seen commonly in multiparous than nullipara or primipara women. Annigeri *et al.* and Mandal *et al.* found that 85.33% of multiparous women were having DUB [2,11]. In some studies like Grover *et al.*, only multiparous women were selected as participants [14].

Among bleeding pattern, menorrhagia was the most common (58.2%). In a study conducted by Annigeri *et al.* and Komaram *et al.*, the common pattern was menorrhagia and was found in 73.16% and 44% of women, respectively [2,15].

45.5% of women were having >8 days of bleeding before intervention which reduced to 2% after intervention. Ormeloxifene has a significant effect on bleeding duration. The same results were seen with Shabab *et al.*, Godha *et al.* [12,16] (mean duration of bleeding reduced to 4.8 from 9), Grover *et al.* [14] (total bleeding days decreased by 76% with treatment), Soniya *et al.* [17] (81.63% of patients got relief from

menorrhagia), and Mandal *et al.* [11] (reduction in menstrual blood flow in 61.11%). Reduction in total bleeding days was indirectly reflected an increase in Hb level.

The regular menstrual pattern was achieved in 87.9% of women. In a study conducted by Grover *et al.*, 66.7% of women achieved regular menses at the end of 3 months' treatment [14]. This number may go up after 6 months of treatment.

In our study, 85.9% of women were having heavy bleeding which reduced to zero at the end of treatment. This finding is in line with a study by Singh *et al.*, in which 53.32% pretreatment value reduced to 4.65% [18].

Passages of clots were significantly reduced to 7.07% from 78.9%. There are many studies which show the result in line with our study. There was a significant improvement in Hb concentration. Mean Hb improved from 9.5 to 10 g/dl. There are several studies which showed near similar results (Table 6).

CONCLUSION

Ormeloxifene is an effective alternative and appears to be a promising option for the medical management of DUB. It has a convenient dosing schedule. Ormeloxifene reduced the duration of bleeding significantly, and menstrual cycle became regular. It showed a positive impact on the amount of bleeding. Passages of clots were reduced and mean hemoglobin was increased. Along with being effective, the drug has a good patient acceptability and compliance and simple dosage schedule.

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AUTHORS' CONTRIBUTIONS

Dr. Umesh Sawarkar and Dr. Sarang Deshmukh have contributed in the initiation of concept, design this study, literature search, data acquisition, and data analysis. Dr. Ashwini Raut and Dr. Uma Bhosale have contributed in statistical analysis and manuscript preparation. Dr. Ashok Shenoy has done manuscript editing and review.

CONFLICTS OF INTEREST

There is no conflict of interest.

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