

A Study of Effect of Ormeloxifene in Dysfunctional Uterine Bleeding and Dysmenorrhoea in Women of Reproductive Age Group

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Abstract

Introduction: Dysfunctional uterine bleeding (DUB) is a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause (Pelvic pathology, e.g. tumor, inflammation or pregnancy is excluded). Ormeloxifene has been evaluated for the management of menorrhagia but was seldom compared with progesterone. This study was an attempt to find out the cost-effectiveness of ormeloxifene against medroxyprogesterone acetate (MPA).

Aims & Objectives: To evaluate the efficacy and side effects of Ormeloxifene in cases of dysfunctional uterine bleeding and dysmenorrhoea in women of reproductive age group and compare it with Medroxyprogesterone Acetate.

Materials & Methods: 100 women of reproductive age group attending the gynaecology out patients department satisfying inclusion criteria were enrolled for this study, which was done over a period of one year (June 2016 to May 2017) in the Department of Obstetrics and Gynaecology, Bardhaman Medical College & Hospital. 50 women randomly selected were given Ormeloxifene & the rest 50 women were given Medroxyprogesterone Acetate.

Results: Significant reduction of post-treatment menstrual blood loss, dysmenorrhoea, endometrial thickness & drug related side-effects among Ormeloxifene group compared to Medroxyprogesterone group. Ormeloxifene is more cost-effective than Medroxyprogesterone acetate.

Conclusion: Ormeloxifene is suitable for the treatment of dysfunctional uterine bleeding and dysmenorrhoea in women of reproductive age group with effective therapeutic efficacy, convenient dosage schedule, lesser side-effects and more cost-effectiveness compared to Medroxyprogesterone Acetate.

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I. Introduction

Dysfunctional uterine bleeding (DUB) is a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause (Pelvic pathology, e.g. tumor, inflammation or pregnancy being excluded). It is typically characterised by heavy, prolonged flow with or without breakthrough bleeding. DUB is a diagnosis that does not apply to menorrhagia only, but also includes excessively prolonged and frequent bleeding (Menometrorrhagia). It occurs more frequently in anovulatory than ovulatory cycles.

Even though a number of treatment modalities are available, a reliable drug for management of dysfunctional uterine bleeding should meet the requirements like 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. Ormeloxifene (also known as Centchroman) is one of the selective estrogen receptor modulators or SERMs, a class of medications which act on the estrogen receptor (ER). It is a non-steroidal non-hormonal oral contraceptive which is taken once in a week. It mediates its effects by high affinity interaction with ER, antagonising the effect of Estrogen on uterine and breast tissue and stimulating effect on vagina, bone, cardiovascular system and central nervous system. Ormeloxifene not only preferred as oral contraceptive, but also useful for management of dysfunctional uterine bleeding, mastalgia and advanced breast cancer. In the pharmacological management of DUB the standard dose is 60 m.g. orally twice weekly for a period of 12 weeks, followed by once in a week, for the next 12 weeks. The safety profile of Ormeloxifene is excellent with very few side effects like nausea, headache, weight gain, delayed or prolonged menstrual bleeding. To the best

of our knowledge very few studies are available on Ormeloxifene for the treatment of DUB. We have therefore proposed to verify the efficacy of Ormeloxifene in the management of DUB in 20-40 years aged women.

Cyclical therapy of Medroxyprogesterone Acetate (MPA) is also used in 5th to 25th day course twice daily orally in DUB. It reduces menstrual blood loss by 50%.

Ormeloxifene has been evaluated for the management of menorrhagia but was seldom compared with progesterone. This study was an attempt to find out the cost-effectiveness of ormeloxifene against medroxyprogesterone acetate (MPA).

II. Aims & Objectives

To evaluate the efficacy and side effects of Ormeloxifene in cases of dysfunctional uterine bleeding and dysmenorrhoea in women of reproductive age group and compare it with Medroxyprogesterone Acetate. To evaluate endometrial histopathology of patients on Ormeloxifene after 3 months of treatment, and to record side effects and patient compliance.

III. Materials & Methods

Study Design: Prospective Randomised Controlled Trial conducted in the Department of Gynaecology and Obstetrics in Burdwan Medical College and Hospital from June 2016 and continued till May 2017.

Study Population : Total study group of 100 women of reproductive age group attending Gynaecology O.P.D. of B.M.C.H. Ormeloxifene was given to 50 patients. MPA was given to another 50 patients.

Inclusion Criteria:

Women of reproductive age group.

Complaining of excessive, prolonged or frequent interval of bleeding .

Dysmenorrhoea.

Exclusion Criteria:

Postmenopausal bleeding.

Endometrial biopsy suggestive of atypical hyperplasia or malignancy.

Severe cervical dysplasia or carcinoma of cervix.

Fibroid uterus/Adenomyosis/Endometrial polyp/cervical polyp.

Study Method and Statistical Analysis:

Subjects were recruited from O.P.D. of Obstetrics and Gynaecology Department, after taking informed consent and using proper randomization method for allocation in one of the arms of study. Detailed history of menstrual problems was taken. General examination was done to assess the anemia and obesity and to rule out signs and symptoms of bleeding disorders, hypothyroidism and jaundice. A pelvic examination was done to rule out pregnancy, fibroid, adenomyosis or any other pathology. Baseline Investigations were conducted for Hb%, T.L.C., D.L.C., B.T., C.T., Platelet count, Prothimbin Time, P.B.S. & T.S.H. to rule out bleeding dyscrasias and occult hypothyroidism. A T.V.S. was done for Endometrial thickness and other pathology. Ormeloxifene was administered orally in the form of 60 m.g. tablet twice weekly (every Sunday and Thursday) for the first 12 weeks and then once a week (every Sunday) for another 12 weeks in 50 patients. Medroxyprogesterone Acetate was administered orally In the form of 10 m.g. tablet twice daily from day 5 to day 25 of cycle for 3 consecutive cycles in another 50 patients. Patients were told to keep a record of their menstrual blood loss including number of days of bleeding, number of pads soiled and degree of soiling , history of passage of clots and dysmenorrhoea. Patients were followed up every 30 days. Two pre-treatment baseline cycles were compared to the treatment cycles of Ormeloxifene and MPA .

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes. Continuous variables are expressed as Mean \pm Standard Deviation and compared across the 2 groups using unpaired t test. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

IV. Results

Table 1: Pictorial Blood Assessment Chart in Pretreatment and Post treatment

	Group		p Value	Significance
	Ormeloxifene	Medroxyprogesterone Acetate(Mpa)		
PBAC Pre Tt	234.72 \pm 61.37	229.68 \pm 58.67	0.676	Not Significant
PBAC Post Tt	90.65 \pm 18.07	106.75 \pm 32.45	0.008	Significant

There was no significant difference ($p > 0.05$) in pre-treatment PBAC score among Ormeloxifene group and Medroxyprogesterone group. But our study shows significant reduction ($p < 0.05$) of post treatment PBAC score among Ormeloxifene group compared to Medroxyprogesterone group.

Figure 1: Pictorial Blood Assessment Chart in Pre-treatment and Post-treatment showing comparison between two groups

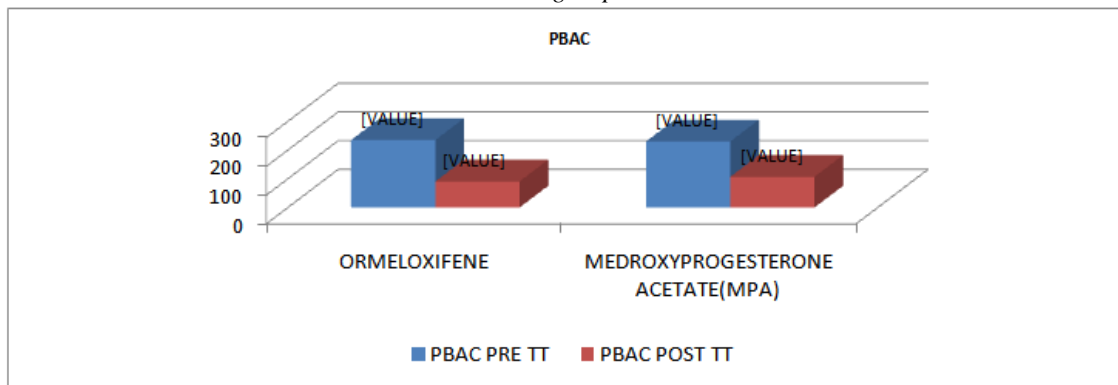


Table 2: Comparison of visual analogue scores in pre-treatment and post treatment among two groups VAS (Visual Analogue Score) was used in our study to measure dysmenorrhoea. Our study shows significant reduction ($p < 0.05$) in post treatment VAS score among Ormeloxifene group compared

	Group		p Value	Significance
	Ormeloxifene	Medroxyprogesterone Acetate(Mpa)		
VAS pre tt	Mean \pm Std. Deviation 6.5 \pm 1.62	Mean \pm Std. Deviation 6.6 \pm 1.44	0.745	Not Significant
VAS post tt	2.58 \pm 0.9	3.83 \pm 0.9	<0.001	Significant

to Medroxyprogesterone group

Figure 2: Visual analogue scores in pretreatment and posttreatment among two groups showing curve of reduction of VAS

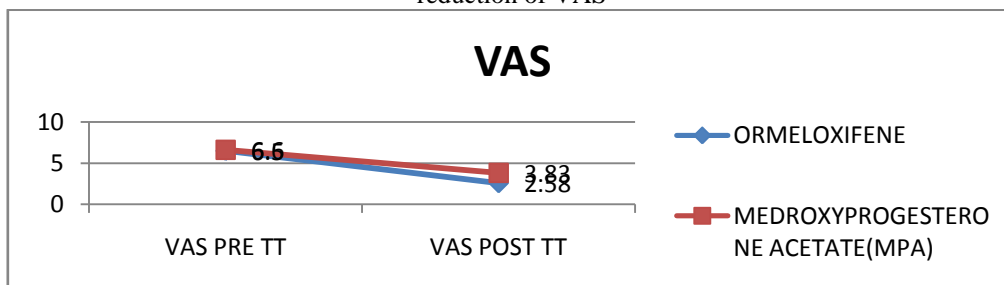


Table 3: Comparison of Endometrial Thickness (ET) in pre-treatment and post treatment among two groups

	GROUP		p Value	Significance
	Ormeloxifene	Medroxyprogesterone Acetate(Mpa)		
ET (mm) pre tt	Mean \pm Std. Deviation 9.21 \pm 2.63	Mean \pm Std. Deviation 9.16 \pm 2.5	0.916	Not Significant
ET (mm) post tt	4.05 \pm 1.22	5.09 \pm 1.29	<0.001	Significant

There was no significant difference ($p > 0.05$) in pre-treatment endometrial thickness among the two groups. Our study shows significant decrease in post treatment endometrial thickness ($p < 0.05$) in the patients treated with Ormeloxifene compared to the patients treated with Medroxyprogesterone Acetate.

Figure 3: Endometrial Thickness (ET) in pre-treatment and post treatment among two groups showing curve of decrease in post treatment ET

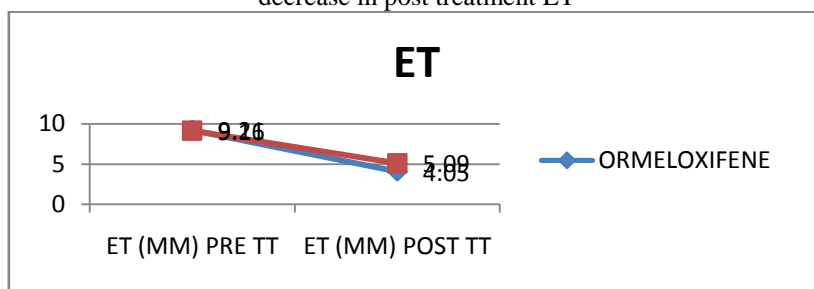
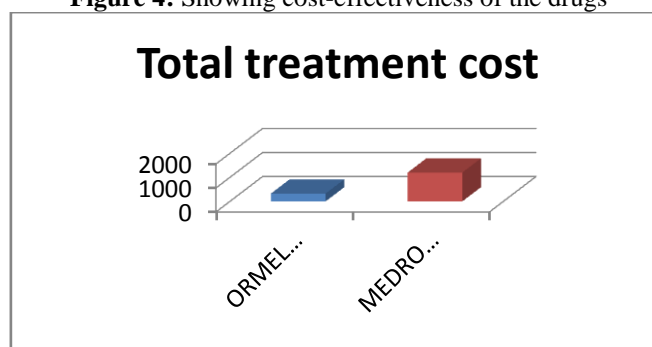


Table 4: Showing cost-effectiveness of the drugs:

	Tab. Ormeloxifene	Tab. Medroxyprogesterone Acetate
Dosage schedule	1 tablet(60mg) twice weekly for 1 st 3 months followed by 1 tablet(60mg) once weekly for next 3 months.	1 tablet (10mg) twice daily for 20 days × 6 cycles.
Duration of treatment	6 months	6 months
Total tablets required	36	240
Cost of the drug	Tab. Sevista 1 strip = 8 tablets(60mg)=Rs.72.40/- (1\$)	Tab. Deviry 1 strip= 10 tablets(10mg)=Rs.42/- (0.6\$)
Total cost of treatment	Rs.325.80/- (4.6\$)	Rs.1008/- (14.2\$)

Figure 4: Showing cost-effectiveness of the drugs



V. Discussion

One hundred O.P.D. patients presented with DUB (dysfunctional uterine bleeding) were divided equally and randomly between the two groups. Twelve patients were later excluded for failure to comply with prolonged follow up, 2 in Ormeloxifene group and 10 in Medroxyprogesterone group. Further analysis was focussed on the 88 patients who completed the study. The patients were then randomly allocated to one of two groups: Ormeloxifene group and Medroxyprogesterone Acetate group. In Ormeloxifene group number of patients in 18-20 years were 7(14%), in 21-30 years were 22 (44%), in 31-40 years were 15 (30%), in 41-50 years were 6 (12%). In Medroxyprogesterone group number of patients in 18-20 years were 5 (10%), in 21-30 years were 23 (46%), in 31-40 years were 15 (30%), in 41-50 years were 7 (14%). In both the group most of the patients were 21-30 years aged. A study was conducted on dysfunctional uterine bleeding in J N Medical College, Belgaum. A sample of 100 cases of clinically diagnosed dysfunctional uterine bleeding were analyzed clinically and supplemented by histological studies. It reveals that this condition is common in reproductive age group (58%) and perimenopausal (38%).¹ Among 100 patients in our study, 70% patients presented with acyclic bleeding, and 30% patients presented with cyclic bleeding. DUB can be classified by anovulatory bleeding (represented by acyclic bleeding) and ovulatory bleeding (represented by cyclic bleeding). Among them anovulatory bleeding is most common.²

The mean pretreatment menstrual blood loss (PBAC score) in Ormeloxifene group was 234.72± 61.37(156-368) which reduced to 90.65 ± 18.07(64-124) by the end of 6 months. The mean pretreatment menstrual blood loss (PBAC score) in Medroxyprogesterone group was 229.68 ± 58.67 (154-364) which reduced to 106.75 ± 32.45 (70-158). There was significant reduction in menstrual blood loss in patients

on Ormeloxifene ($p = 0.008$). Kripalini et al³ conducted a pilot study in which the median PBAC score was significantly reduced from 338 to 88 at 2 months and to 5 at 4 months with a 99.7% reduction in mean blood loss. Our study shows the mean pretreatment VAS in Ormeloxifene group was 6.5 ± 1.62 (3-9) which was reduced to 2.58 ± 0.9 (1-4) by the end of 6 months and in Medroxyprogesterone Acetate group the mean pretreatment VAS was 6.6 ± 1.44 (4-9) which was reduced to 3.83 ± 0.9 (2-5) after 6 months treatment. Reduction in VAS in Ormeloxifene group after 6 months of treatment was statistically significant ($p < 0.001$), compared to Medroxyprogesterone Acetate. Improvement in dysmenorrhoea in Ormeloxifene group was observed in 60.3% patients in this study as against 81.8% and 78.3% in Laxmi⁴ et al and Biswas⁵ et al study respectively. Our study shows pretreatment mean endometrial thickness in Ormeloxifene group was 9.21 ± 2.63 (4.6-14.4) which was reduced to 4.05 ± 1.22 (2-6.6) after 6 months of treatment. In Medroxyprogesterone group pretreatment mean endometrial thickness was 9.16 ± 2.5 (5-15), after 6 months of treatment the mean endometrial thickness became 5.09 ± 1.29 (3-8.1). This study shows significant reduction of endometrial thickness ($p < 0.001$) after treatment with Ormeloxifene for 6 months compared to Medroxyprogesterone. Dhananjay⁶ et al studied 35 patients with DUB and found a statistically significant decrease in endometrial thickness (9.83 to 4.89; $p < 0.001$) after 3 months of treatment with Ormeloxifene. In Bhawna⁷ et al study there was a significant reduction of endometrial thickness from 8.36 to 4.89 ($p < 0.001$). In Biswas⁵ et al study using Ormeloxifene in DUB showed significant reduction in endometrial thickness after 6 months of treatment.

In our study, commonest side-effects noted in Medroxyprogesterone group were acne (8%), breast tenderness (6%), break through bleeding (28%), insomnia (6%), spotting (40%), weight change (8%). No obvious side effects were noted in 12% of patients of this group. The commonest side effects noted in Ormeloxifene group were delayed menstruation (48%) and nausea, vomiting (24%). No obvious side effects were noted in 34% of patients of this group. Though the patients become anxious regarding amenorrhoea, if proper counselling is done before prescribing the drug, it is of no concern. In Deepa Masand⁸ et al study, Ormeloxifene was very well tolerated and practically there was no undesirable side effects. Where total cost of the treatment with Medroxyprogesterone Acetate is about Rs. 1008/-, the treatment cost with Ormeloxifene is only Rs.325.80/-. So, Ormeloxifene is more cost-effective than Medroxyprogesterone Acetate in the treatment of DUB.

VI. Conclusion

Ormeloxifene is suitable for the treatment of dysfunctional uterine bleeding and dysmenorrhoea in women of reproductive age group with effective therapeutic efficacy, convenient dosage schedule, lesser side-effects and more cost-effectiveness compared to Medroxyprogesterone Acetate.

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