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Research Article

Comparative evaluation of the efficacy and safety of ormeloxifene and norethisterone in dysfunctional uterine bleeding

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ABSTRACT

Background: Dysfunctional Uterine Bleeding (DUB) is the most common cause of abnormal uterine bleeding and is a major indication for referral to gynecological clinics. There are very few studies comparing the effect of ormeloxifene and progesterone in DUB. The objective of the study was to assess the efficacy and safety of Ormeloxifene in DUB and compare it with Norethisterone.
Methods: Hundred women presenting with DUB were randomly allocated to 2 equal groups, Group-A, which received 60mg ormeloxifene twice a week for 12 weeks followed by 60mg once a week for next 12 weeks and Group-B, which received 5mg norethisterone twice daily for 21 days for 6 cycles. The primary outcomes were reduction in menstrual blood loss [measured by fall in PBAC (Pictorial Blood loss Assessment Chart) score and subjective assessment], rise in hemoglobin level and decrease in endometrial thickness.
Results: The reduction in mean PBAC score with ormeloxifene (216 to 88) was significantly more than with norethisterone (262 to 162) at 3 months ($p<0.01$). The rise in hemoglobin concentration and fall in endometrial thickness were also significantly more with ormeloxifene than norethisterone (7.52g% to 9.2g% vs. 7.48g% to 8.4g%, $p<0.05$, and 12.12mm to 9.46mm vs. 12.05mm to 10.7mm, $p<0.05$, respectively). Further improvement at 6 months was much more with ormeloxifene. No major side effects were reported in any group.
Conclusions: Both drugs are effective in treating DUB, but ormeloxifene is superior to norethisterone in reducing menstrual blood loss.

Keywords: Dysfunctional Uterine Bleeding (DUB), Norethisterone, Ormeloxifene, Selective Estrogen Receptor Modulator (SERM)

INTRODUCTION

Abnormal uterine bleeding includes all cases of uterine bleeding that do not follow typical menstrual pattern. Dysfunctional Uterine Bleeding (DUB) is abnormal uterine bleeding in the absence of any systemic, organic or iatrogenic cause.[1] It is the most common cause of abnormal uterine bleeding which can affect any woman from menarche to menopause, occurring more commonly at the extremes of age. It has several adverse effects, including anemia, reduced quality of life and increased healthcare costs because it is a major indication for referral to Gynecological outpatient clinics.[2]

Menorrhagia (menstrual blood loss >80 ml per cycle) affects 10-33% of women at some stage in their lives.[3] Over 75,000 hysterectomies are carried out every year with 30% of them being done for menstrual disturbances, especially menorrhagia.[4] Though the option is relatively safe with low mortality, one cannot deny the morbidity associated with this modality of treatment. In recent years, concern has been expressed about possible long term complications of hysterectomy like premature ovarian failure, cardiovascular disease and intestinal or urinary dysfunction. Thus, more and more women are looking forward to an effective medical therapy.[5-7]

Antifibrinolytics, non-steroidal anti-inflammatory drugs (NSAIDs), progesterones, combined estrogen and progesterones, danazol, gonadotrophin releasing hormone analogues and levonorgesterol-releasing intrauterine system have all been used with different results. Norethisterone, a progestogen, is commonly used for this purpose but being a hormonal drug, it is associated with side effects such as stroke, heart disease, breast cancer, dementia, fluid retention, breakthrough bleeding, spotting etc.

Ormeloxifene, a third generation Selective Estrogen Receptor Modulator (SERM) selectively acts on estrogen receptors as agonist and antagonist in different reproductive tissues.[8] It has anti-estrogenic action on endometrium and breast and estrogenic action on bones, vagina, liver, cardiovascular and central nervous system. The ideal therapy in perimenopausal women is one that has no uterine stimulation, prevents bone loss, has no risk of breast cancer, has a positive effect on lipids and cardiovascular system and maintains cognitive function of brain. SERM in general and ormeloxifene in particular satisfy these requirements.[9,10]

Unlike progesterone, ormeloxifene does not produce spotting, breakthrough bleeding or menorrhagia. Clinical studies have shown the effectiveness of ormeloxifene in DUB, but there are very few studies comparing the effect of ormeloxifene and progesterone in DUB.

The aim of this study was to assess the efficacy and safety of ormeloxifene in DUB and to compare it with norethisterone.

METHODS

This is a prospective comparative study conducted in the Department of Obstetrics and Gynecology, S.N Medical College, Agra, in which 100 women presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause were recruited. Ethical approval was taken from the institutional ethical committee. Exclusion criteria were pregnancy, bleeding disorders, medical disorders- liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism, and lactating women in first 6 months of post natal period.

Informed consent was taken. A detailed history and examination was done. DUB is a diagnosis of exclusion. Investigations were done to rule out any other possible cause for abnormal uterine bleeding. These were complete blood cell count including hemoglobin (Hb) level, pregnancy test, thyroid stimulating hormone, coagulation profile, pap smear, pelvic ultrasound (to measure endometrial thickness and rule out any pelvic pathology) and endometrial sampling for histopathological assessment.

The cases were asked to maintain a menstrual diary recording the days of bleeding, number of sanitary pads used, degree of soiling of each pad, number and size of clots passed, episodes of bleeding, the presence of menstrual cramps and other symptoms experienced. A Pictorial Blood loss Assessment Chart (PBAC) Scoring was done accordingly to assess menstrual blood loss (Table 1). PBAC is a simple and less time consuming procedure for objective assessment of menstrual blood loss, which does not require collection of sanitary products and avoids costly chemical analysis. A PBAC score ≥ 100 indicates a menstrual blood loss ≥ 80ml and is considered diagnostic for menorrhagia.[11]

Table 1: PBAC Scoring.[11]

Pads	Lightly soiled	1
	Moderately soiled	5
	Saturated	20
Clots	Small (smaller than a rupee coin)	1
	Large (larger than a rupee coin)	5

The women were randomly allocated to 2 groups of 50 each. Group A was given Ormeloxifene tablet 60mg twice a week for 12 weeks followed by 60mg once a week for next 12 weeks. Group B was given Norethisterone tablet 5mg twice a day for 21 days followed by 7 days withdrawal for 6 cycles. Follow up was done at 1, 3 and 6 months. At each visit a detailed menstrual history was taken, PBAC score was calculated and hemoglobin concentration and endometrial thickness were measured. Subjective improvement and any side effects experienced were also noted.

The primary outcome measures were reduction in amount of menstrual blood loss (assessed by fall in PBAC score and patient's subjective assessment), rise in hemoglobin concentration and decrease in endometrial thickness in proliferative phase on transvaginal ultrasound. Secondary outcome measures were the side effects.

All continuous efficacy parameters were presented as Mean ± Standard Deviation and were analyzed using the student t test. Statistical significance was taken at $p \leq 0.05$.

RESULTS

The cases in both the groups matched well with regards to mean age, parity, socioeconomic status and duration of symptoms. The pretreatment mean PBAC score, mean hemoglobin level and mean endometrial thickness were also comparable in both the groups (Table 2). The most common presenting complaint was menorrhagia (60% in group A and 64% in group B). Proliferative endometrium was the most common endometrial pattern in both groups followed by cystic glandular hyperplasia (Table 3).

Table 2: Clinical profile and parameters before starting therapy.

Clinical parameters	Group A (Ormeloxifene) n=50	Group B (Norethisterone) n=50	*p* value
Mean age (years)	38.3	39.1	> 0.05
Mean parity	3	3	> 0.05
Socioeconomic status	III	III	> 0.05
Mean duration of symptoms (months)	9.4	9.6	> 0.05
Mean PBAC score	216	232	> 0.05
Mean Hb level (gm%)	7.52	7.48	> 0.05
Mean endometrial thickness (mm)	12.12	12.05	> 0.05

Table 3: Endometrial patterns on histopathology.

Endometrial patterns	Group A (Ormeloxifene) n=50		Group B (Norethisterone) n=50	
	No.	Percentage (%)	No.	Percentage (%)
Proliferative	19	38	18	36
Cystic glandular hyperplasia	17	34	17	34
Secretory	10	20	12	24
Irregular ripening	3	6	2	4
Irregular shedding	1	2	1	2
Total	50	100	50	100

Table 4: Comparison of Ormeloxifene and Norethisterone.

Outcome measures	Pretreatment (n=50)	After 3 months of therapy (n=50)	After 6 months of therapy (n=50)	*p* value
Mean PBAC score				
Ormeloxifene	216	88	84	<0.01
Norethisterone	232	162	170	
Mean Hb level (gm%)				
Ormeloxifene	7.52	9.2	10.4	< 0.05
Norethisterone	7.48	8.4	8.6	
Mean endometrial thickness (mm)				
Ormeloxifene	12.12	9.46	8.4	< 0.05
Norethisterone	12.05	10.7	9.8	

Table 4 shows the comparison of ormeloxifene and norethisterone with respect to outcome measures.

The mean pretreatment PBAC score with ormeloxifene was 216 which was significantly reduced to 88 after 3 months of therapy and to 84 after 6 months of therapy ($p<0.01$). The mean pretreatment PBAC score with norethisterone was 232 which was significantly reduced to 162 after 3 months of therapy followed by a marginal increase to 170 at 6 months ($p<0.01$). On comparing both the groups, reduction in PBAC score was more with ormeloxifene and the difference was statistically significant ($p<0.01$). Eighty percent of women had a PBAC score <100 at 3 months with ormeloxifene as compared to only 30% with norethisterone.

The pretreatment mean hemoglobin concentration in group A was 7.52gm% which was significantly increased to 9.2gm% at 3 months and further increased to 10.4 gm% at 6 months with ormeloxifene ($p<0.01$). The pretreatment mean hemoglobin concentration in group B was 7.48gm% which was significantly increased to 8.4gm% at 3 months with only a slight further increase to 8.6gm% at 6 months with norethisterone ($p<0.01$). On comparing both the groups, rise in hemoglobin level was more with ormeloxifene and the difference was statistically significant ($p<0.05$).

The mean endometrial thickness (as measured in proliferative phase by trans-vaginal sonography) was significantly reduced from 12.12mm to 9.46mm after 3

months and further reduced to 8.4mm after 6 months of therapy with ormeloxifene (p<0.01). With norethisterone, the mean endometrial thickness was significantly reduced from 12.05mm to 10.7mm after 3 months and to 9.8mm after 6 months of therapy (p<0.01). On comparing the two groups, reduction in endometrial thickness was more with ormeloxifene and the difference was statistically significant (p<0.05).

Reduction in menstrual blood loss in both the groups was more in perimenopausal women having thicker endometrium on ultrasound and endometrial hyperplasia on histology, but the reduction was more with ormeloxifene.

The fall in PBAC score was maximum in cases having cystic glandular hyperplasia in both the groups followed by proliferative and secretory pattern. The cases having irregular ripening and shedding did not respond well to either therapy.

Eighty-eight percent of cases showed marked subjective improvement with ormeloxifene as compared to 74% with norethisterone. There was no improvement in 6% cases with ormeloxifene as compared to 14% with norethisterone. There was no worsening of symptoms in either group (Table 5).

Table 5: Subjective assessment of improvement.

Subjective improvement	Group A (Ormeloxifene) n=50		Group B (Norethisterone) n=50	
	No.	Percentage (%)	No.	Percentage (%)
No improvement	3	6	7	14
Mild improvement	3	6	6	12
Marked improvement	44	88	37	74
Worsening of symptoms	0	0	0	0
Total	50	100	50	100

Although there were no major side effects, 8% cases receiving ormeloxifene had amenorrhea, 8% had hypomenorrhea and 4% developed nausea, vomiting and headache. Four percent cases receiving norethisterone had breakthrough bleeding and 14% cases had spotting.

DISCUSSION

Menorrhagia accounts for most of the referrals to the Gynecological clinics and in majority of the cases no organic pathology is identified. The exact mechanism of DUB is uncertain but is believed to be caused by dysfunction of hypothalamic-pituitary-ovarian axis.[12] Although a number of drugs are available, there is a general lack of evidence-based approach, marked variation in practice and continuing uncertainty regarding the most appropriate therapy.[1]

In the present study, the reduction in menstrual blood loss (as assessed by fall in PBAC score and patient's subjective assessment), rise in hemoglobin concentration and decrease in endometrial thickness were significantly more with ormeloxifene than norethisterone after 6 months of therapy. The results were significant even after 3 months of therapy. There were no major side effects with either of the drugs.

In a similar study, Bhattacharjee et al[7] used similar dose of ormeloxifene with a shorter duration of norethisterone of 10 mg daily for 12 days (from 14th day) in each cycle as compared to 21 days in our study. They too found ormeloxifene to be superior to norethisterone in reducing menstrual blood loss. The reduction in mean PBAC score was significant in both groups but was more with ormeloxifene (108.7 to 62.48) than norethisterone (113.8 to 94.07). The increase in hemoglobin concentration occurred maximally with ormeloxifene. The reduction in endometrial thickness was significant but similar in both groups. There was marked improvement in 81.67% cases on ormeloxifene, which was comparable to 88% in the present study, but in only 35% cases on norethisterone, which was much less than our study (74%). They found no improvement in 10% cases on ormeloxifene and 29% on norethisterone as compared to 6% and 14% in our study. Amenorrhea, hypomenorrhea, spotting, stress urinary incontinence and uterovaginal prolapse were observed with ormeloxifene and breakthrough bleeding and spotting were seen with norethisterone. A larger study to validate these deleterious side effects observed by ormeloxifene in their study is required.

The present study showed a 61.1% reduction in menstrual blood loss with ormeloxifene as compared to only 26.7% with norethisterone. Shravage et al[13] compared ormeloxifene to another progesterone, medroxy progesterone acetate. They found an 85.7% reduction in menstrual blood loss with ormeloxifene as compared to 54.76% with medroxy progesterone acetate. The reduction in mean endometrial thickness was more with ormeloxifene, however this difference was not statistically significant, maybe because of shorter period of observation of 3 months. Kriplani et al[14] found a 99.7% reduction in median PBAC score in 4 months. Side effects like ovarian cyst, cervical erosion and discharge, gastric dyspepsia, vague abdominal pain and headache occurred in a few women.

Similar to the present study, Dhananjay et al[15] found a statistically significant increase in hemoglobin concentration (8.26 to 10.59g/dl; p<0.001) and a statistically significant decrease in the endometrial thickness (8.36 to 4.89mm; p<0.001) after 3 months of treatment with ormeloxifene. Dadhich et al[1]and Biswas et al[16] also found a significant reduction in median PBAC score, number of days of menstruation and number of

sanitary napkins used after 6 months of ormeloxifene therapy.

Amenorrhea / hypomenorrhea is a common symptom seen with ormeloxifene in different studies with a wide range of 8% to 63%.[1,7,16] It is more common in perimenopausal women. However, with proper counseling, the women find it a desirable symptom at this age.

In the present study, the most common endometrial pattern was proliferative followed by cystic glandular hyperplasia and secretory endometrium. However, Kriplani et al[14] found secretory endometrium to be the most common pattern followed by proliferative and simple hyperplasia without atypia.

CONCLUSIONS

Dysfunctional uterine bleeding is a common gynecological problem. Majority of the patients respond well to medical therapy. Both ormeloxifene and progesterone (norethisterone) are effective in treating these cases as studied by reduction in PBAC score, subjective improvement, rise in hemoglobin level and reduction in endometrial thickness. However, the effect is significantly more with ormeloxifene. Thus, ormeloxifene was found to be superior to norethisterone in reducing menstrual loss. There are no major side effects or complications with either of the drugs. A convenient dose schedule and cost effectiveness of ormeloxifene further increases its compliance.

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