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The Efficacy and Safety of Ormeloxifene in Dysfunctional Uterine Bleeding

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Abstract: *The study was undertaken to assess the efficacy, safety and acceptability of ormeloxifene in the medical management of Dysfunctional Uterine Bleeding (DUB). Sixty women with DUB were given ormeloxifene 60mg twice a week for 12 weeks and once a week for next 12 weeks. Follow up was done at 3 and 6 months. The primary outcome measures were menstrual blood loss, hemoglobin concentration and endometrial thickness. The secondary outcome measures were the acceptability and side effects of ormeloxifene. There was a significant reduction in the menstrual blood loss as measured by median PBAC scores pre and post treatment. The median PBAC score was significantly reduced from 334 to 111 after 3 months and to 32 after 6 months ($p < 0.0001$) The mean pretreatment Hb concentration was significantly increased from 9.04gm% to 10.01 gm% at 3 months and to 10.86 gm% at 6 months ($p<0.0001$).The mean pretreatment endometrial thickness was reduced from 11.35mm to 9.4 mm after 3 months of therapy and to 8.13 mm after 6 months ($p<0.0001$). 88.3% women showed marked subjective improvement in symptoms. There were no major side effects. Ormeloxifene, with its convenient dose schedule, is an effective and safe alternative in the management of dysfunctional uterine bleeding.*

Keywords – *Dysfunctional Uterine Bleeding (DUB), Menorrhagia, Ormeloxifene, Selective Estrogen Receptor Modulator (SERM)*

I. Introduction

Dysfunctional Uterine Bleeding (DUB) is a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause. It is the most common menstrual disorder of women in reproductive age and is a diagnosis of exclusion. It can affect any woman from menarche to menopause, occurring more commonly at extremes of age.

Menorrhagia (menstrual blood loss >80 ml per cycle) affects 10-33% of women at some stage in their lives [1]. Medical management of menorrhagia is a challenging task and wide variations in the available drugs prescribed for this condition show a lack of consensus for medical treatment [2]. The medical options for initial management of DUB include antifibrinolytics, nonsteroidal anti-inflammatory drugs (NSAIDs), combined estrogen and progesterones or progesterones alone, high dose estrogens, gonadotropin-releasing hormone agonists, danazol and levonorgesterol releasing intrauterine systems. Cyclical combined oral contraceptive pills were widely used previously but side effects have limited their use in DUB. Danazol, progesterone and gonadotropin-releasing hormone analogs are all effective in terms of reducing menstrual blood loss but adverse effects and costs limit their long term use [3].

Selective Estrogen Receptor Modulators (SERMs) selectively bind with high affinity to estrogen receptors and act as estrogen agonists in some tissues and estrogen antagonists in others. Ormeloxifene, a third generation SERM, antagonizes the effect of estrogen on uterine and breast tissue and stimulates its effect on vagina, bone, cardiovascular and central nervous system [4].Thus, it is especially beneficial in perimenopausal women as it has no uterine stimulation, prevents bone loss, does not increase the risk of breast cancer, lowers cholesterol level and maintains cognitive function of the brain. It has the additional advantage of reducing premenstrual symptoms, mastalgia and dysmenorrhea. When ormeloxifene (centchroman) was used as a contraceptive, its beneficial effect on menorrhagia and endometriosis was observed, which led to controlled trials for the management of menorrhagia after its approval for this indication.

The aim of the present study was to assess the efficacy, safety and acceptability of ormeloxifene in the medical management of dysfunctional uterine bleeding.

II. Methodology

This prospective study was conducted in the Department of Obstetrics and Gynaecology, S.N Medical College, Agra over a period of one year. Sixty women with Dysfunctional Uterine Bleeding (DUB) were recruited from the Gynaecological OPD. The diagnosis of DUB was made after excluding other possible causes of abnormal uterine bleeding. The exclusion criteria were pelvic pathologies like uterine fibroids, suspected adenomyosis, malignancies of uterus/cervix/ovary/vagina/endometrial hyperplasia with atypia; medical diseases

like – liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism, platelet disorders or coagulopathy, previous history of thrombosis; pregnancy, abortion, use of IUCDs or oral contraceptives; lactating women in first 6 months of post-natal period and hypersensitivity to the drug.

Informed consent was taken. All cases were given ormeloxifene 60mg twice a week for 12 weeks and then once a week for next 12 weeks. Follow up was done at 3 months and 6 months or earlier if needed. The primary outcome measures were menstrual blood loss, hemoglobin concentration and endometrial thickness in proliferative phase by trans-vaginal sonography (TVS). The secondary outcome measures were the acceptability and side effects of ormeloxifene.

Menstrual blood loss was objectively assessed by Pictorial Blood loss Assessment Chart (PBAC) [5], which correlates well with the alkaline hematin test [6]. Subjective assessment of the improvement of symptoms was also done. The women were given instructions on how to do PBAC scoring according to the degree of soiling of sanitary napkins and number and size of clots passed (Table 1). A PBAC score ≥ 100 is equivalent to menstrual blood loss ≥ 80ml and is considered diagnostic of menorrhagia [5].

Table 1: PBAC Scoring

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

PBAC score, hemoglobin concentration and endometrial thickness were measured before the start of therapy, at 3 months and at 6 months. A detailed menstrual history (number of days of menstruation, number of sanitary napkins used, passage of clots, dysmenorrhea) and physical examination was done at each visit. Any side effects observed were noted. The subjective improvement of symptoms and acceptability of ormeloxifene were also inquired.

All continuous efficacy parameters were presented as Mean ± Standard Deviation and Median (Range) and were analyzed using the paired t test. The Chi square and Fisher's exact test were used as appropriate for independent nominal data. Statistical significance was taken at $p \leq 0.05$.

III. Observations and Results

Sixty women with the diagnosis of DUB were recruited for the study; with a PBAC score more than 100 in the pretreatment cycles. Table 2 shows the clinical profile of the study group. The mean age of the women was 32.8 years, mean parity 3.5 and the mean duration of symptoms was 11.5 months.

Table 2: Clinical profile of women

S.No.	Clinical parameter	Mean (Range)
1.	Age (years)	32.8 (20-50)
2.	Parity	3.5 (2-7)
3.	Duration of symptoms (months)	11.5 (6-20)

Menstrual blood loss (assessed by PBAC score), hemoglobin level and endometrial thickness were observed before starting treatment and then after 3 and 6 months of treatment. The outcome measures at 3 months are shown in Table 3 and at 6 months are shown in Table 4.

Table 3: Outcome measures of the study (after 3 months)

S.No.	Outcome parameter	Pre-treatment	Post-treatment (3months)	p value
1.	Median PBAC score	334	111	p<0.0001 (t=15.25)
2.	Mean hemoglobin level (gm%)	9.04	10.01	p<0.0001 (t=20.38)
3.	Mean endometrial thickness (mm)	11.35	9.4	p<0.0001 (t=24.27)
4.	Presence of clots	46/60 (76.7%)	20/60 (33.3%)	p<0.0001
5.	Dysmenorrhea	17/60 (28.3%)	11/60 (18.3%)	p=0.280

Table 4: Outcome measures of the study (after 6 months)

S.No.	Outcome parameter	Pre-treatment	Post-treatment (6months)	p value
1.	Median PBAC score	334	32	p<0.0001 (t=16.63)
2.	Mean hemoglobin level (gm%)	9.04	10.86	p<0.0001 (t=34.42)
3.	Mean endometrial thickness (mm)	11.35	8.13	p<0.0001 (t=23.53)
4.	Presence of clots	46/60 (76.7%)	9/60 (15%)	p<0.0001
5.	Dysmenorrhea	17/60 (28.3%)	4/60 (6.7%)	p=0.0032

The median pre-treatment PBAC score was 334 with a range of 123-643. After 3 months of treatment with ormeloxifene it was reduced to 111 (range 42-201) and after 6 months to 32 (range 0-75). The reduction was extremely statistically significant ($p < 0.0001$) at both intervals. Thus there was a 90.42% reduction in the menstrual blood loss after 6 months of therapy.

Presence of clots is an obvious evidence of abnormally excessive flow as reported by Higham et al [5]. In the present study 80.43% (37/46) cases showed improvement by absence of clots at the end of the therapy. Ormeloxifene also had a beneficial effect in reducing the occurrence of dysmenorrhea.

Most of the women were anemic, with 49 (81.67%) women having a hemoglobin level less than 10 gm%. The mean pretreatment Hemoglobin concentration was 9.04 gm% (range 7.3-11gm%). It was significantly increased to 10.01 gm% at 3 months (range 8.4-11.7gm%; $p<0.0001$) and further increased to 10.86 gm% at 6 months (range 9.3-12.4gm%; $p<0.0001$). Thus there was significant increase in mean hemoglobin concentration of 1.82 gm% after 6 months.

The mean pretreatment endometrial thickness as measured by TVS in the proliferative phase was 11.35 mm with a range of 8-17mm. It was reduced to 9.4 mm after 3 months of therapy (range 6-13mm; $p< 0.0001$) and to 8.13 mm after 6 months (range 4-11mm; $p<0.0001$). The reduction was statistically significant.

The women were asked about the subjective improvement of symptoms as shown in Table 5. Majority (88.3%) showed marked improvement in symptoms. Two women had no improvement of symptoms; however there was no aggravation of symptoms in any woman. Ormeloxifene was acceptable to 96.67% women.

Table 5: Subjective assessment of symptoms

S.No.	Subjective improvement	Number	Percentage (%)
1.	No improvement	2	3.33
2.	Mild improvement	5	8.33
3.	Marked improvement	53	88.33
4.	Aggravation of symptoms	0	0
	Total	60	100

There were no major side effects. Amenorrhea was the most common symptom, seen in 17 women (28.3%). Out of these, 15 women were ≥ 40 years and only 2 were < 40 years. Nausea vomiting (6.67%) and headache (5%) were other side effects but neither was significant enough to stop the therapy.

IV. Discussion

Menorrhagia accounts for most of the referrals to the Gynaecological OPD and in majority of the cases no organic pathology is identified. DUB reflects a disruption in the normal cyclic pattern of ovulatory hormonal stimulation to the endometrial lining. It is considered a diagnosis of exclusion. 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 [3].

In the present study, our results suggested that there was a significant reduction in menstrual blood loss with ormeloxifene, as assessed by fall in PBAC score and patient's subjective assessment. There was also a significant rise in hemoglobin concentration and a significant decrease in endometrial thickness after 6 months of therapy. The results were significant even after 3 months of therapy. Ormeloxifene was acceptable to most of the women. The safety profile of ormeloxifene is very good with no major side effects. A few side effects which occurred were mild gastrointestinal symptoms (6.67%) and headache (5%). Amenorrhea was seen in 17 women (28.3%), most of them perimenopausal.

The present study showed a 90.42% reduction in menstrual blood loss. Kriplani et al conducted a pilot study in which the median PBAC was significantly reduced from 388 to 80 at 2 months and to 5 at 4 months

with a 99.7% reduction ($p<0.001$). Side effects like ovarian cyst, cervical erosion and discharge, gastric dyspepsia, vague abdominal pain and headache occurred in a few women [7].

Similar to the present study, Dhananjay et al 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 [8].

Shravage et al found an 85.7% reduction in menstrual blood loss (a fall in mean PBAC score from 262 to 73) after 3 months of therapy. They found that ormeloxifene was more effective than medroxy progesterone acetate in the treatment of DUB [9]. Dadhich et al also found a significant reduction in median PBAC score (379 to 15), number of days of menstruation and number of sanitary napkins used after 6 months of ormeloxifene therapy [3].

Biswas et al found that the difference between pretreatment and post-treatment median PBAC score of 97.2 and the rise in mean hemoglobin concentration of 1.31 g/dl was statistically significant ($p<0.001$). In the present study the rise in mean hemoglobin concentration was 1.82 gm% (from 9.04 to 10.86 gm%) [4].

Amenorrhea was a common symptom seen in different studies with a wide range of 8% to 42.9% [3-5,8,9]. It is more common in perimenopausal women However, with proper counseling the women do not find it bothersome, in fact it is welcomed by them. Majority of women (88-92%) have complete relief with ormeloxifene [3]. Some women do not respond to ormeloxifene and require an alternative treatment. The percentage varies from 4 – 16.7% [3-5] in various studies as compared to 3.33% in the present study.

V. Conclusion

Ormeloxifene is effective and quick acting (usually bleeding is controlled in 2-3 days) and appears to be a promising option for the medical management of DUB. It leads to a significant reduction in menstrual blood loss, a significant rise in hemoglobin concentration and a significant decrease in endometrial thickness without any major side effect. It has a convenient dose schedule of once or twice a week and is cost effective. It can be used in any age group and is oncologically protective to the breast and endometrium. It is well tolerated and a safe alternative for medical management of DUB.

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