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Original Research Article

Efficacy of ormeloxifene in comparison to oral contraceptive pills in medical management of dysfunctional uterine bleeding

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ABSTRACT

Background: Menstrual disorders are the most common gynecological condition resulting in hospital referrals. Dysfunctional Uterine Bleeding is an abnormal uterine bleeding, in the absence of any organic, systemic or iatrogenic cause. Among women in reproductive age, one in 20 consults her general practitioner each year with menorrhagia. This condition can be managed both medically and surgically. Pharmacological treatment options available for DUB are combined oral contraceptive pills, progestogens, danazol, gonadotrophin releasing hormone (GnRH) agonists, prostaglandin synthetase inhibitor, anti-fibrinolytics and ethamsylate. Role of ormeloxifene in dysfunctional uterine bleeding (DUB) is still in an exploring level. The purpose of the study was to evaluate the efficacy of ormeloxifene in the treatment of DUB and compare the effects of ormeloxifene with combined oral contraceptive pills for the control of DUB.

Methods: Sixty women presenting with DUB were randomly allocated to 2 equal groups, Group A were given ormeloxifene tablet @ 60 mg twice a week for 12 weeks, followed by 60 mg once a week for 12 weeks. Group B were given low dose combined oral contraceptive pills (OCP) containing 30 microgram ethinyloestradiol and 150 microgram levonorgestrel from day 1 to day 21st of the menstrual cycle for 6 cycles. The various parameters studied were reduction in menstrual blood loss which was measured by fall in pictorial blood loss assessment chart (PBAC) score, rise in haemoglobin (Hb) level and reduction in endometrial thickness, any drug side effects, compliance with the drug, dosage schedule and effect on quality of life after each month and at the end of trial period of 6 months. Patient's level of satisfaction was assessed by improvement in Hb concentration, sense of wellbeing as well as overall general health, quality of life, sexual life and comfort with the continuation of the same drug.

Results: Mean blood loss (PBAC score) following treatment showed significant reduction in both the groups, however this reduction was comparatively high in ormeloxifene treated group. The various parameters to assess the subjective and clinical improvement at the end 3 and 6 months post treatment showed significant improvement in both the treatment groups; however ormeloxifene group showed significantly better improvement in comparison to OCP group. Mean endometrial thickness also showed reduction in both the groups but more significant reduction was observed in ormeloxifene group as compared to OCP group following 6 months of treatment. Symptomatic relief and subjective feelings in relation to improvement of menstrual abnormalities, any undesirable side effects, about dosage compliance and any thought of discontinuing the drug by the patients indicated excellent control of menorrhagia in both the study group, which accounted for 86.66% in ormeloxifene group and 80% of individuals in OCP group.

Conclusions: ORM is effective in control of DUB and can be used as an alternative to OCP for treatment of DUB with possibly minimal side effects and better dosage compliance.

Keywords: Dysfunctional uterine bleeding, Oral contraceptive pill, Ormeloxifene, PBAC score, Endometrial thickness, Dosage compliance

INTRODUCTION

Abnormal uterine bleeding is defined as, bleeding of any cause which does not follow a typical menstrual pattern in relation to frequency, duration of bleeding or amount of blood loss. The normal menstrual cycle comprises of regular, cyclical uterine bleeding at the interval of 21-35 days, the flow lasting for 2-6 days and a blood loss of 20-80 ml.[1] The cause of uterine bleeding may be structural and associated with pathology in the genital organs. It can be hormonal due to disturbance in functioning of the Hypo-thalamo-pituitary–ovarian (HPO) axis or it may be because of various coagulopathies.[2]

Dysfunctional uterine bleeding (DUB)is an abnormal uterine bleeding, in the absence of any organic, systemic or iatrogenic cause.[2] DUB can affect more commonly at extremes of reproductive ages when the function of HPO axis is either immature or starts ceasing and becomes irregular. So, DUB is mostly caused by hormonal imbalance. It has several adverse effects including anaemia, reduced quality of life and increased healthcare cost. It is a major cause for referral to gynaecological outpatient clinics and account for one of the major cause for hysterectomies with added risk of surgical and anaesthetic complications.[3,4]

Many articles have reviewed the management of DUB and often include use of algorithms to manage it in stepwise manner, starting from medical therapy to minimally invasive surgeries to hysterectomy.[1,5,6] Pharmacological interventions can be hormonal or non-hormonal. Hormonal agents include oestrogen, progesterone, combined oral contraceptive pills (OCP), danazole, GnRH agonists, levonorgestrel containing IUCD(Mirena) and more recently ormeloxifene, a selective oestrogen receptor modulator (SERM). Non hormonal group include NSAID, ethamsylate and antifibrinolytics. The ACOG recommends to start the treatment with medical therapy failing which resort to surgical treatment.[3,6]

Oral contraceptive pills (OCP) are commonly used for treatment of DUB in adolescent and reproductive age group but having oestrogen as a component it is contraindicated in patients with hypertension, current or past history of venous thromboembolism, ischemic heart disease, history of cerebrovascular accident, complicated valvular heart disease, smokers, patients with severe migraine headache, focal neurological signs, breast cancer, diabetes with retinopathy and neuropathy, liver disease etc.[7]

Ormeloxifene is a third generation selective oestrogen receptor modulator (SERM), which acts selectively on oestrogen receptors on bones, vagina, liver, cardiovascular and central nervous system and as antagonist on endometrium and breast.[8-10] It does not produce spotting or breakthrough bleeding.[11]

The ideal therapy in peri-menopausal women is one that has no stimulatory effects on endometrium, prevents bone loss, no risk of breast cancer, positive effect on lipids and cardiovascular system and no adverse effect like abnormal menstrual bleeding. Ormeloxifene satisfy all these criteria.

With this background the present study was carried out to evaluate the efficacy of ormeloxifene in the treatment of DUB and compare the results with combined oral contraceptive pills.

METHODS

A prospective comparative study was conducted in the department of obstetrics and gynaecology, Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, India with prior approval from institutional ethical committee. Informed consent was obtained from all the participants in the study. 60 patients were selected for the study comprising of 30 in each group. Group A belonged to ormeloxifene and Group B belonged to OCP. A detailed history, physical examination and relevant clinical investigations were performed to rule out any organic, hormonal or haematological cause for abnormal uterine bleeding since DUB is a diagnosis by exclusion. Transvaginal ultrasound was done and endometrial biopsy was obtained from each patient. Pap's smear was collected and whenever necessary, hysteroscopy was also done. Coagulation profile, thyroid profile, urine beta hCG was also performed, whenever required. Haemoglobin level was checked for all the patients.

Patients with known pelvic pathologies like fibroids, endometriosis, malignancy of genital tract, medical diseases like liver dysfunction, heart diseases, renal diseases, coagulopathies, thyroid disorders, IUCD or pill users, pregnant or lactating women and women already on treatment for DUB were excluded from the present study.

- Group A were given ormeloxifene tablet @ 60 mg twice a week for 12 weeks, followed by 60 mg once a week for 12 weeks.
- Group B were given low dose combined oral contraceptive pills (OCP) containing 30 microgram ethinyloestradiol and 150 microgram levonorgestrel from day 1 to day 21st of the menstrual cycle for 6 cycles.

Patients were advised to use same kind of sanitary napkins with similar absorptive capacity and maintain menstrual calendar to chart, number of days bleeding occurred, number of pads used, degree of soiling of pads, number and size of passage of clots, if any. History of inter-menstrual spotting or bleeding or any other symptoms during premenstrual, inter-menstrual or postmenstrual phase were advised to record. Objective assessment of blood loss was obtained by using 'pictorial

blood loss assessment chart' (PBAC) as shown in Table 1 based on the above mentioned data.[12]

Table 1: PBAC scoring system.

PBAC scoring system	
Sanitary Napkins	Mildly soiled-1
	Moderately Soiled- 5
	Completely Saturated- 20
Clots	Small- 1
	Large- 5

A 'PBAC' score of >100 suggests a blood loss of >80 ml and indicates menorrhagia.

Though the patients were asked to maintain menstrual calendar each month, the main treatment outcome was measured at 3 and 6 month interval after the start of the therapy. The parameters used to compare were mean menstrual blood loss, mean Hb concentration and endometrial thickness in proliferative phase (measured by transvaginal ultrasound).

Patient were also interviewed for any drug side effects, compliance with the drug, dosage schedule and effect on quality of life after each month and at the end of trial period of 6 months. Patient's level of satisfaction was assessed by improvement in Hb concentration, sense of wellbeing as well as overall general health, quality of life, sexual life and comfort with the continuation of the same drug.

Statistical analysis

The data collected was analysed and comparison of values between the groups was performed using students "t". Statistical significance was considered at p value <0.05. Column charts are used to compare values across categories.

RESULTS

The present study was conducted on 60 individuals, which comprised of 70% married and 30% unmarried women. The parity status showed 61.66% as multiparous and 38.33% were nulliparous as given in Table 2.

The socio-demographic and clinical parameters in both the treatment groups were almost similar except for the minor differences in a few studied variables. When comparing the post treatment results the mean blood loss (PBAC score) following treatment showed significant (p <0.05) reduction in both the groups, however this reduction was comparatively on higher side in ormeloxifene group as in Table 3. Histopathological examination of endometrial tissue before the start of treatment showed significantly higher cases of proliferative phase in comparison to secretory and simple hyperplasia of endometrium in both the treatment groups as shown in Figure 1.

Table 2: Marital status and parity status of patients.

Marital status	No. of Patients	Percentage
Married	42	70
Unmarried	18	30
Parity Status		
Multi-para	48	61.66
Nulli-para	12	38.33

Table 3: Socio-demographic and pre-treatment clinical parameters of patients.

Clinical Parameters	Group A ormiloxifene (n=30)	Group B OCP (n=30)
Mean Age	35.2	34.6
Mean Parity	2	2
Social class	III	III
Mean Duration of Menorrhagia (months)	12.77	12.44
Mean Duration of Bleeding (Days)	8.6	8.4
Mean Duration of Cycle length	29.33	30
Mean PBAC score	218	216
Mean Hb (g%)	8.6	8.4
Mean Endometrial thickness (mm)	10.8	11

The various parameters to assess the subjective and clinical improvement at the end 3 and 6 months post treatment showed significant improvement in both the treatment groups, however ormeloxifene group showed significantly (P <0.05) better improvement in comparison to OCP group as given in Table 4). Mean endometrial thickness also showed reduction in both the groups but more significant (P <0.05) reduction was observed in ormeloxifene group as compared to OCP group following 6 months of treatment as in Table 4.

The data presented in Table 5 on symptomatic relief and subjective feelings in relation to improvement of menstrual abnormalities, any undesirable side effects, about dosage compliance and any thought of discontinuing the drug by the patients indicated excellent control of menorrhagia in both the study group, which accounted for 86.66% (P <0.05) in ormeloxifene group and 80% of individuals in OCP group.

Side effects of the therapy were also recorded in both the treatment groups (26.66% in ormeloxifene and 33.33% in OCP group). Patients in group a reported amenorrhoea as the main side effect and nausea, vomiting and headache reported by few subjects. Participants of OCP users reported nausea, vomiting, mild premenstrual breast tenderness and mild weight gain and intermenstrual spotting per vaginum. Overall, none of the participants from either of the group reported intolerable side effects.

Although 4 patients from the OCP group reported no improvement of symptoms, however none of the patients discontinued the treatment before the end of the study period as given in Table 5.

Table 4: Comparision of ormeloxifene with OCP in different groups at various interval following treatment.

Parameters	Pre-treatment	After 3 months	After 6 months	P value
Mean PBAC Score				
Group A	218	74	50	<0.05
Group B	216	126	88	
Mean Hb%				
Group A	8.6	10.6	11.2	<0.05
Group B	8.4	9.6	10	
Mean endometrial thickness				
Group A	10.8	8	6	<0.05
Group B	11	10.5	8	

Table 5: Subjective and clinical improvement of symptoms in patients of various groups at the end of treatment.

Subjective improvement	Ormeloxifene		OCP	
	Number of patient	Percentage	Number of patient	Percentage
No improvement	0	0	4	13.33
Satisfactory	4	13.33	6	20
Excellent	26	86.66	24	80
Side effect	8	26.66	10	33.33
Discontinued	0	0	0	0

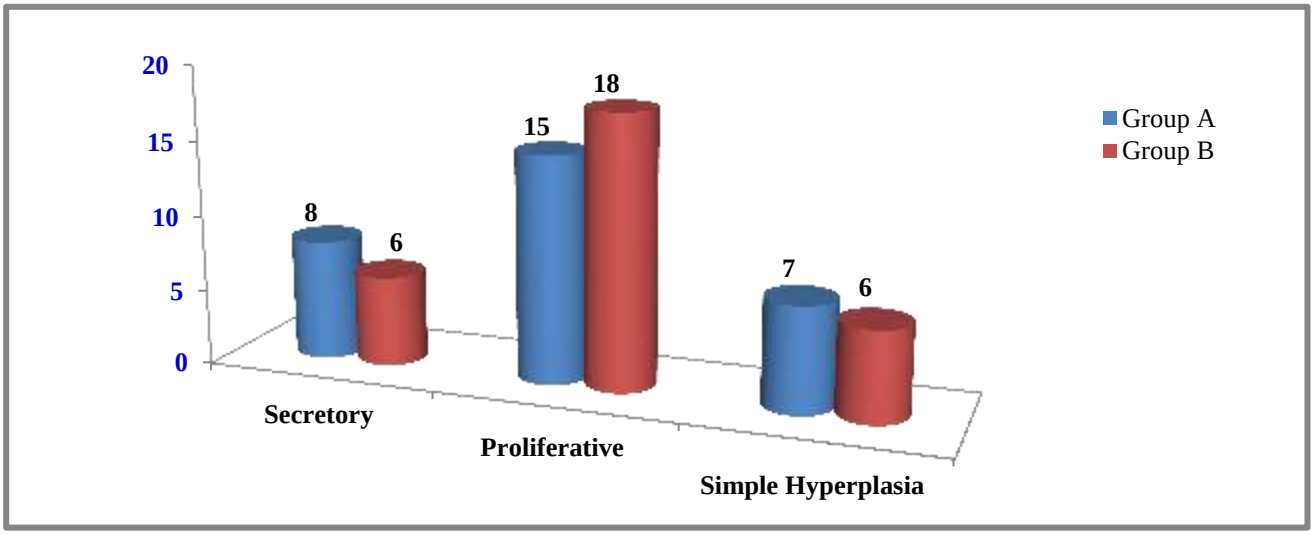

Figure 1: Comparison of endometrial pattern in patients following treatment with ormeloxifene (group A) and OCP (group B).

DISCUSSION

Dysfunctional uterine bleeding is defined as abnormal uterine bleeding without organic and systemic pathology or iatrogenic causes.[2,13] Studies suggest that changes in hormonal milieu is responsible for DUB. Though this ailment is most commonly observed near the beginning and end of women's reproductive life, but may occur at any time.[1] There are medical, surgical or combined methods for treatment of DUB and the choice of approach depends on the cause, severity of bleeding, patient's desire for fertility, need for contraception and available treatment options. One of the most important goals in workup of DUB is to rule out neoplastic conditions of endometrium. Hence before beginning any therapy, endometrial biopsy is a must, especially in older women. Many authors have reviewed the management of DUB and suggested treatment algorithms.[13,5] ACOG guidelines recommend that surgery should be considered only in patients wherein medical treatment has failed,

cannot be tolerated or is contraindicated. Many drugs have been recommended for treatment of DUB including antifibrinolytics, medroxyprogesterone acetate, NSAIDs, oral contraceptive pills, progestins, levo-norgestrel containing IUCD, GnRH analogues, danazol and a few studies have also recommended use of ormeloxifene.[1,3,5,11,14,15]

In the present study, reduction in menorrhagia represented by decrease in post-treatment PBAC score was significantly observed in both the treatment groups, however, ormeloxifene treatment showed better results in comparison to OCP.

In a similar study conducted earlier, the mean PBAC score at pre-treatment and 6 months post-treatment with ormeloxifene treatment was found to be 174 and 75, respectively. The same score was recorded as 174 and 106, respectively following oral contraceptive pills.[7]

The results of present study with regard to PBAC score following treatment with ormeloxifene and OCP are comparable with the earlier studies conducted to treat dysfunctional uterine bleeding using similar drugs.[15]

The significant rise in mean haemoglobin level observed in individuals of both the treatment groups in the present study is in corroboration with the findings of earlier studies following treatment with ormeloxifene and OCP.[3,7,11,15-17] The mean endometrial thickness was also significantly reduced in both the study groups following therapy. At the end of 6 months post treatment with ormeloxifene showed better results on reduction of ET in comparison to OCP therapy and these findings are in agreement with the earlier studies.[3,11]

Though in the present study, the level of satisfaction among the patients was observed in both the treatment groups, however ormeloxifene therapy was reported to be comparatively more effective. The side effects were minimal and tolerable in both the groups indicated the safety and tolerance of both the drugs among all the patients.

In both the groups, level of satisfaction among the patients with the treatment was high, 88.66% in ormeloxifene and 80% in OCP group. 26% cases reported side effects with ormeloxifene treated group whereas 33.33% in OCP group. The side effects were minimal and tolerable in both the groups. Patients treated with ormeloxifene reported mild nausea, vomiting and occasional headache. Amenorrhea was the main reported side effects with ormeloxifene. OCP users reported nausea, vomiting, premenstrual breast tenderness and mild weight gain. Chhatrala et al reported that satisfaction level following treatment with ormeloxifene was observed in 68.6% and with OCP in 47% cases.[7] Minimal side effects were observed with both the group of the present study are in agreement with earlier report.[15]

CONCLUSION

The present study concludes that, ormeloxifene and OCP are almost equally effective for the treatment of DUB as evident by control of menorrhagia, increased haemoglobin concentration and reduced endometrial thickness as well as patient's satisfaction level with slight superiority of ormeloxifene. In the view of positive results, the present study recommends ormeloxifene as a choice for treatment of DUB and can be used as an alternative to OCP for treatment of DUB with possibly minimal side effects and better dosage compliance.

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