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ORIGINAL ARTICLE

Study of Efficacy and Safety of Ormeloxifene in the Management of Dysfunctional Menorrhagia

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ABSTRACT

Objective: To assess the efficacy and safety of ormeloxifene in the medical management of dysfunctional menorrhagia.

Methodology: Fifty women with menorrhagia were recruited for the study. Ormeloxifene 60 mg twice a week for 3 months from first day of periods and once a week for next 3 months was given. Mean blood loss (MBL) was assessed using pictorial blood loss assessment chart (PBAC). Ultrasonography (USG) and blood hemoglobin levels were done as baseline and at 2, 4 and 6 months of treatment. Side-effects of the drug were recorded. Changes in PBAC scoring, endometrial thickness (ET) and hemoglobin levels (Hb) were analyzed by student's paired 't' tests using SPSS 17.0 version. p value ≤ 0.05 was taken as significant.

Results: The pretreatment PBAC score was 360, which reduced to 209.5 at 2 months, 88.7 at 4 months and 68.2 at 6 months of treatment, which was statistically significant (p-value ≤0.001). The rise in hemoglobin and decrease in ET, in women on ormeloxifene was also statistically significant (p-value ≤0.001).

Conclusion: Ormeloxifene is an effective and safe therapeutic option for the medical management of menorrhagia.

Keywords: Dysfunctional uterine bleeding, Menorrhagia, Ormeloxifene.

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INTRODUCTION

Menorrhagia is defined as menstrual blood loss of at least 80 ml per cycle or a pictorial blood loss assessment chart score of more than 100.[1] Menorrhagia affects 10 to 33% women during their lifetime and accounts for 5% of all gynecologic consultations each year. A large proportion of women with menorrhagia will subsequently undergo a hysterectomy. Medical management is required for those wishing to conserve fertility or nearing menopause. Ormeloxifene is a nonsteroidal, nonhormonal selective estrogen receptor modulator (SERM). It has antiestrogenic action on uterus and breast, estrogenic action on vagina, bones, cardiovascular system and central nervous system.

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METHODOLOGY

After ethical approval, the study was conducted in the Department of Obstetrics and Gynecology, Era's Lucknow Medical College, Lucknow, India. Sixty-one patients presenting with menorrhagia (PBAC ≥ 100) were clinically evaluated. Hemogram and ultrasound (to rule out any pelvic pathology and to measure endometrial thickness) were performed in all the patients. Hysteroscopy was performed when transvaginal ultrasound revealed endometrial thickness more than 8 mm or a suspicion of endometrial polyp. Endometrial aspirations were performed in all patients. Exclusion criteria included uterine size more than 8 weeks, pelvic pathology like uterine fibroids, polyps, adnexal mass, systemic coagulation disorder, renal or hepatic dysfunction, history of infertility and known endocrinopathy.

Six patients were excluded from the study (two-tuberculous endometritis, one-hyperplasia with atypia, three-small fibroid on USG). Fifty five patients were enrolled for the study after obtaining a written informed consent. Five patients were lost to follow-up and data of 50 patients was analyzed. Baseline information regarding symptomology, duration of cycle and PBAC scoring were collected. Ormeloxifene was given in dose of 60 mg twice a week for 3 months from first day of periods and once a week for next 3 months. No hormone or any other agent to control menorrhagia was prescribed during this period. Patients were asked to maintain a menstrual diary and to come for monthly follow-up. An arbitrary PBAC score of 10 or less was defined as scant flow, between 10 and 100 was defined as moderate flow, more than 100 was defined as heavy bleeding, and more than 300 was defined as very heavy bleeding. Hemoglobin levels and ultrasound were repeated at 2nd, 4th and 6th months of treatment.

Outcomes analyzed were change in PBAC scoring, endometrial thickness, hemoglobin levels, compliance to treatment and adverse effect profile.

STATISTICAL ANALYSIS

Changes in bleeding days, PBAC scoring, endometrial thickness and hemoglobin levels were analyzed by student's paired 't' tests using SPSS 17.0 version. p-value ≤ 0.05 was taken as significant.

RESULTS

Patient Profiles

The mean age of the study population was 37.94 ± 6.63 years (29-51). Majority (80.4%) of the women were multiparous, nine (19.6%) were primiparous. The median duration of menorrhagia was 17.26 ± 9.52 months (4-40 months). The median duration of bleeding days was 7 days (4-30) and median cycle length was 25 days (17-30).

Histopathology

Endometrial aspiration revealed secretory endometrium in 21 women (42%), proliferative in 15 (30%), simple hyperplasia without atypia in five cases (10%).

Response on duration of Bleeding and MBL

The mean pretreatment MBL (PBAC score) was 360 (170-735), which reduced to 209.5 (100-400) at 2 months and 88.7 (0-370) at 4 months with treatment. By end of 6 months, the mean PBAC score was 68.2 (0-400). There was a significant reduction in MBL in patients on ormeloxifene (p-value ≤ 0.001) (Graph 1 and Table 1). There was reduction in cases of moderate dysmenorrhea (15.2%) from pretreatment value of 21.7% and severe dysmenorrhea from a pretreatment value of 8.7 to 2.2% (Table 2).

Hemoglobin Level

The rise in the mean hemoglobin level at the end of 2 months of treatment was 9.78 ± 1.14 gm% (8-12.4 gm%) compared to the pretreatment level of 9.30 ± 1.27 gm% (7-11.4 gm%). At 4 months of therapy, mean hemoglobin of the study group was 10.64 ± 0.90 gm% (8-12.3 gm%). The rise in hemoglobin rise at the end of 2 and 4 months of treatment was significant (p-value ≤ 0.001) (*see* Table 1).

ENDOMETRIAL THICKNESS

The mean endometrial thickness in the pretreatment group was 8.58 ± 2.13 mm (4-12 mm). There was decrease in mean ET at 2 months (7.28 ± 2.33 mm), 4 months (5.58 ± 1.86 mm) and 6 months (5.68 ± 1.97 mm) of treatment. The decrease in ET was found to be statistically significant (p-value ≤ 0.001) (*see* Table 1).

Compliance

Out of 55 patients who were recruited for the study, five patients were lost to follow-up. All of these were outstation patients.

Adverse Effects

Adverse effects included gastric upset (five cases: 10%), vague abdominal pain (three cases: 6%) and headache (seven cases: 14%). Twenty-four patients (48%) did not respond.

DISCUSSION

Dysfunctional uterine bleeding is the diagnosis in a majority of the cases of menorrhagia. The symptom of menorrhagia accounts for a significant proportion of the referrals to gynecologists. Menorrhagia is usually defined as menstrual blood loss of at least 80 ml per cycle or a pictorial blood loss assessment chart score of more than 100.[1] Though the gold standard for assessment of blood loss is alkaline hematin method, we preferred to use PBAC score as it is simple, less time consuming method and cost effective. Mean blood loss levels correlate well with PBAC scores.[1]

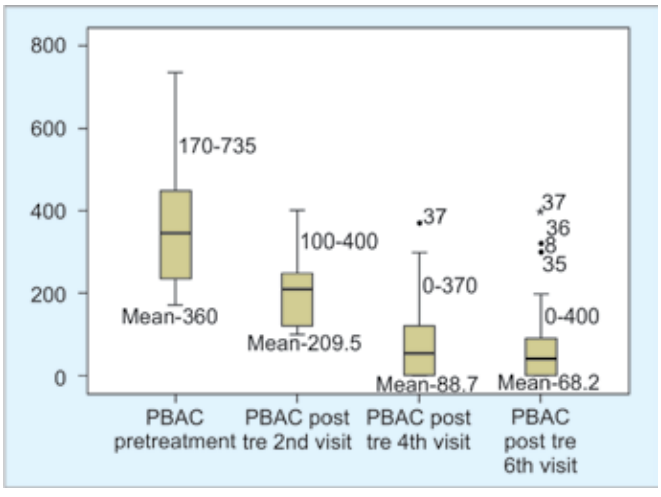
Medical treatment of menorrhagia should aim to relieve symptoms, improve quality of life and avoid the risk of surgery. The options available include NSAIDs, antifibrinolytics, daily hormonal pills, levonorgestrel intrauterine system

Table 1: Outcome measurements of PBAC, mean hemoglobin and endometrial thickness

n = 50	*Pretreatment*	*Post-treatment (2nd month)*	*Post-treatment (4th month)*	*Post-treatment (6th month)*	*Remarks*
Mean PBAC (ml)	170-735 (mean-360)	100-400 (mean-209.5)	0-370 (mean-88.7)	0-400 (mean-68.2)	p ≤ 0.001
Mean Hb (g/dl)	9.30 ± 1.27 (7-11.4g/dl)	9.78 ± 1.14 (8-12.4g/dl)	10.64 ± 0.90 (8-12.3g/dl)	–	p ≤ 0.001
Mean ET (mm)	8.58 ± 2.13 (4-12 mm)	7.28 ± 2.33 (4-12 mm)	5.58 ± 1.86 (1-11 mm)	5.68 ± 1.97 (1-12 mm)	p ≤ 0.001

Table 2: Dysmenorrhea pre- and post-treatment. n = 50

		Pretreatment		*Post-treatment*	
		No.	*%*	*No.*	*%*
Dysmenorrhea present	Mild	17	37	20	43.5
	Moderate	10	21.7	7	15.2
	Severe	4	8.7	1	2.2
	Total	31	68.9	28	62.2
Dysmenorrhea absent		14	30.4	17	37.0



Graph 1: Box plots showing serial PBAC during follow-up

(LNG-IUS) and selective estrogen receptor modulators (SERMS). Despite a decrease in MBL by 50%, many women remain menorrhagic when treated with tranexamic acid, mefenemic acid, flurbiprofen, norethisterone or ethamsylate and many are noncompliant due to daily dosing. The role of levonorgestrel intrauterine system in menorrhagia is well-established and 80% reduction in MBL is seen, but its cost limits its widespread use, especially in developing countries, such as India.[2,3]

Ormeloxifene (3,4,-trans-2,2-dimethyl-3-phenyl-4-p-(b pyrrolidinoethoxy)-phenyl-7-methoxy chroman), synthesized at the Central Drug Research Institute, Lucknow, is a nonsteroidal once a week oral contraceptive. It was introduced in Delhi in July, 1991, marketed in India in 1992 (Saheli/Choice-7/Centron), and included in the National Family Welfare Programme in 1995. It is approved by Indian Drug Regulatory authorities for use in dysfunctional uterine bleeding.

Ormeloxifene has a long terminal serum half life of 168 hours in women and exhibits duration of anti-implantation/estrogen antagonistic action of 120 hours in the rat.[4] In lactating women, it is excreted in milk in quantities considered unlikely to cause any deleterious effect on suckling babies.[4]

The contraceptive action of ormeloxifene is primarily by its effect on the endometrium. Ormeloxifene induced effects might produce asynchrony between endometrial and embryo development resulting in implantation failure. It does not affect the hypothalamo pituitary axis and does not inhibit ovulation in the subjects.[4,5] Besides contraceptive benefits, ormeloxifene has also shown to reduce incidence of breast cancer, fibroadenoma of breast, epithelial ovarian cancer, endometrial cancer, pelvic inflammatory disease, ectopic pregnancy, benign breast disease, iron deficiency anemia and formation of functional ovarian cysts. Ormeloxifene also has antiresorptive effect on osteoclasts thus preventing osteoporosis. It boosts humoral immunity and also has anti-oxidant effect.[6]

In our study, the menstrual blood loss was significantly reduced in women using ormeloxifene during 2,4 and 6 months follow-up (p-value $\leq$ 0.001). Number of cases with moderate to severe dysmenorrhea also decreased on treatment with ormeloxifene. There was a significant rise in hemoglobin levels from the pretreatment value (p-value $\leq$ 0.001). The decrease in endometrial thickness on USG was also found to be statistically significant (p-value $\leq$ 0.001). Adverse effects included gastric upset (five cases: 10%), vague abdominal pain (three cases: 6%) and headache (seven cases: 14%). Twenty-four patients (48%) in the study group did not respond.

These finding were similar to the previous studies. Kriplani et al[7] conducted a pilot study on 42 patients with menorrhagia. The PBAC was significantly reduced at 2 and 4 months follow-up (p-value < 0.001). Seven patients (16.7%) had no response and three (7.1%) discontinued treatment before 4 months. Hysterectomy was required in 21% patients. Adverse effects included ovarian cyst (7.1%), cervical erosion and discharge (7.1%), gastric dyspepsia (4.8%), vague abdominal pain (4.8%) and headache (4.8%). Dhananjay et al[8] studied 35 patients with DUB and found a statistically significant increase in the Hb g/dl (p-value < 0.001) and a statistically significant decrease in the endometrial thickness (p-value < 0.001) after the treatment with sevista. Biswas et al[9] studied 85 patients and found statistically significant improvement in PBAC score and rise in hemoglobin levels (p-value < 0.001). Endometrial thickness was reduced in 87.05% of the patients. Bhattarcharyya et al[10] studied 180 cases of DUB, who had completed child bearing and were above 35 years. They were randomly assigned to ormeloxifene, progesterone and iron groups. Ormeloxifene group received ormeloxifene for 12 weeks. Norethisterone group received norethisterone for 12 days in every cycle for six cycles. Iron group was given as 60 mg of elemental iron daily. The subjects receiving ormeloxifene experienced a marked improvement (81.7%) in PBAC scores, reduction of blood clots and rise in hemoglobin levels.

Ormeloxifene is an effective and safe option for treatment of DUB. After an initial loading dose of 60 mg twice a week for 12 weeks, patients can be switched to 60 mg once a week dose. Majority of the patients in our study group found dosage regime very convenient. This lead to high patient acceptability and compliance to therapy.

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