NORETHISTERONE VERSUS ORMELOXIFENE IN THE TREATMENT OF PERIMENOPAUSAL DUB

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ABSTRACT

BACKGROUND

Dysfunctional Uterine Bleeding is defined as abnormal uterine bleeding in the absence of organic disease. Regarding the medical management of DUB, several drugs have been used, however there is lack of studies suggesting the most appropriate drug. The objective of the study was to compare the two drugs, Norethisterone a progesterone derivative and Ormeloxifene, a selective oestrogen receptor modulator in terms of effectiveness and safety.

MATERIALS AND METHODS

Women attending Gynaec OPD s with DUB were chosen for the study. Sample size was hundred which was divided in 2 groups**.** Ormeloxifene 60mg twice weekly for 12 weeks followed by once a week for another 12 weeks was given in group A. Group B women received norethisterone 5mg twice a day from day 5 to day 26 of a cycle for 6 months. Primary outcome parameters noted were reduction in menstrual blood loss as measured by fall in PBAC (Pictorial Blood Loss Assessment Chart) score, increase in haemoglobin, and decrease in endometrial thickness at the end of the study.

RESULTS

Ormeloxifene showed a better reduction in mean PBAC score (225 to 75) compared to norethisterone (234 to 110) at 6 months ($p<0.01$). Similarly, group A (Ormeloxifene) showed statistically significant increase in haemoglobin concentration (7.2 g% to 10.5 g% vs. 7.6 g% to 9.9 g%, ($p<0.05$) and reduction in endometrial thickness from 11.8mm to 6.6mm vs. 11.2mm to 8.1mm, $p<0.05$, respectively, in comparison to Group B (Norethisterone). None of the cases reported any major side effects in the study.

CONCLUSION

Ormeloxifene is superior to norethisterone in reducing menstrual blood loss, as well as improving perimenopausal symptoms and thus in the treatment of perimenopausal DUB.

KEYWORDS

Ormeloxifene, Norethisterone, Dysfunctional Uterine Bleeding (DUB), Selective Oestrogen Receptor Modulator, Perimenopausal DUB.

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BACKGROUND

Menstrual disorders are the second most common gynaecological condition resulting in hospital referrals.[1] Dysfunctional Uterine Bleeding is defined as abnormal uterine bleeding in the absence of organic disease.[2] Menorrhagia (menstrual blood loss >80 ml per cycle) affects 10-33% of women at some stage in their lives.[3] It has several adverse effects, including anaemia, reduced quality of life and increased healthcare costs, being a major indication for referral to gynaecological outpatient clinics.[4] It can be managed both medically and surgically. Over 75,000 hysterectomies are carried out every year with 30% of them being done for menstrual disturbances, especially menorrhagia.[5] Though this surgical option is relatively safe, concern has been expressed about possible long-term complications of hysterectomy like premature ovarian failure, cardiovascular disease. In view of the above said complications, women are looking forward to an effective medical therapy in preference to surgical treatments.[5] Pharmacological treatment options available for DUB are combined oral contraceptive pills, progestogens, danazol, gonadotrophin releasing hormone (GnRH) agonists, prostaglandin synthetase inhibitor, anti-fibrinolytics, Ethamsylate and levonorgestrel-releasing intrauterine system. Norethisterone, a progestogen, is commonly used for this purpose but being a hormonal drug,[6] it is associated with side effects such as breast cancer, dementia, fluid retention, breakthrough bleeding, spotting etc.

Ormeloxifene, a third generation Selective Estrogen Receptor Modulator (SERM) selectively acts on oestrogen receptors as agonist and antagonist in different reproductive tissues.[7] It has anti-estrogenic action on endometrium and breast and estrogenic action on bones, vagina, liver,

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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.[8] In the medical management of DUB the dosage of ormeloxifene used is 60 mg orally twice weekly for a period of 12 weeks followed by weekly once for the next 12 weeks. Ormeloxifene is associated with very few side effects like nausea, headache, weight gain, delayed or prolonged menstrual period and with a good safety profile.

Progesterone is known to produce spotting, breakthrough bleeding or menorrhagia, unlike ormeloxifene. The present study was conducted to compare the efficacy and safety of ormeloxifene with norethisterone in the treatment of perimenopausal DUB.

Objective of the Study

The aim of the study was to compare the efficacy of the two drugs ormeloxifene and norethisterone in the treatment of perimenopausal DUB.

MATERIALS AND METHODS

This was a comparative study conducted in the Department of Obstetrics and Gynaecology, Karwar institute of medical sciences, Karwar in which 100 women between 40-55 years presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause were enrolled. Study was carried out for a period of one year.

Ethical approval was obtained from the institutional ethical committee. Informed consent was taken from all the patients. A detailed history and clinical examination was done. As 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 haemoglobin (Hb) level, pregnancy test, thyroid stimulating hormone, coagulation profile, pap smear, pelvic ultrasound (to measure endometrial thickness and rule out any pelvic pathology). The cases were asked to maintain a menstrual diary recording the days of bleeding, number of sanitary pads used, degree of soaking of each pad, number and size of clots passed, and if dysmenorrhoea experienced. The Pictorial Blood-Loss Assessment Chart (PBAC) Scoring was then done accordingly to assess menstrual blood loss. PBAC is a simple procedure for objective assessment of menstrual blood loss.

PADS	Scores
Lightly soiled pads	1
Moderately soiled pads	5
Severely soiled pads	20
CLOTS	**Scores**
Small clots	1
Large clots	5
Flooding	5

Table 1. PBAC Scoring[9]

A PBAC score ≥ 100 indicates a menstrual blood loss ≥ 80 ml and is considered diagnostic for menorrhagia (Table 1).[9]

Women attending Gynaec OPD s with DUB were chosen for the study. Sample size was hundred which was divided in 2 groups with 50 each. Group A was given Ormeloxifene 60mg twice weekly for 12 weeks followed by once a week for another 12 weeks. Group B women received norethisterone 5mg twice a day for 21 days in a cycle for 6 months. Primary outcome parameters noted were reduction in menstrual blood loss as measured by fall in PBAC (Pictorial Blood Loss Assessment Chart) score, increase in haemoglobin, and decrease in endometrial thickness at the end of 3 months and 6 months. At each visit a menstrual history was taken, and PBAC score was calculated. Haemoglobin concentration and endometrial thickness were measured after 3 months and 6 months of the treatment. Patients were asked for side effects.

The parameters were presented as Mean ± Standard Deviation. Statistical analysis was done using the student t test. Statistical significance was taken at p ≤0.05.

Inclusion Criteria

All the women between age 40-55 years presenting with DUB.

Exclusion Criteria

- Organic causes like fibroid uterus, adenomyosis, atypical endometrial hyperplasia.
- Pregnancy.
- Bleeding disorders.
- Medical disorders like liver dysfunction, heart disease, migraine, stroke, renal disease and thyroid dysfunction.

RESULTS

The cases in both the groups were comparable with regards to mean age, parity .No significant differences were noted in both the groups. (Table 2).

Clinical Parameters	Group A (N=50)	Group B (N=50)	P Value
Mean age	48	44	>0.05
Mean parity	2	2	>0.05

Table 2. Age Wise, Parity Distribution of the Subjects

Subjects were comparable with regards to age, parity between the two groups. No significant differences were noted between the two groups.

Clinical Parameters	Group A (n=50)	Group B (n=50)	p Value
Mean Hb level	7.2	7.6	>0.05
Mean Duration of symptoms(months)	8.7	8.2	>0.05
Mean PBAC score	225	234	>0.05
Mean endometrial thickness (mm)	11.8	11.2	>0.05

Table 3. Clinical Parameters in Both the Groups Before Starting Treatment

The most common presenting complaint was menorrhagia (60% in group A and 64% in group B). Haemoglobin levels, PBAC scores, and endometrial thickness between the two groups were comparable before the start of the study and no significant differences were noted.

	PBAC before treatment	PBAC after treatment at 3 months	PBAC at 6 months	P value
Group A (Ormeloxifene) (n=50)	225	98	75	<0.01
Group B (Norethisterone) (n=50)	234	140	110	<0.01

Table 4. Reduction in PBAC After Treatment

After treatment group A showed reduction in PBAC score from 225 to 98 at 3 months and 75 after 6 months (p value <0.01). Group B showed reduction in PBAC score from 234 to 140 at 3 months and 110 after 6 months (p value <0.01). Both the groups showed marked reduction in PBAC scores post treatment, although reduction was more in group A patients treated with ormeloxifene and the difference was statistically significant (p<0.01).

	Baseline Hb	Hb after 3 months	Hb after 6 months	P Value
Group A (ormeloxifene)	7.2	9.1	10.5	0.001
Group B (Norethisterone)	7.6	8.8	9.9	0.002

Table 5. Haemoglobin Levels after Treatment

The pretreatment mean haemoglobin concentration in group A was 7.2 gm% which was significantly increased to 9.1 gm% at 3 months and further increased to 10.5 gm% at 6 months with ormeloxifene (p<0.01). The pretreatment mean haemoglobin concentration in group B was 7.6 gm% which was significantly increased to 8.8 gm% at 3 months with further increase to 9.9 gm% at 6 months with norethisterone (p<0.01). On comparing both the groups, rise in haemoglobin level was more with ormeloxifene and the difference was statistically significant (p<0.05).

	ET before Treatment	ET at 3 Months	ET at 6 Months	P Value
Group A	11.8	9.0	6.6	<0.01
Group B	11.2	10	8.1	<0.01

Table 6. Endometrial Thickness (ET) after Treatment

The mean endometrial thickness (as measured in proliferative phase by trans-vaginal sonography) was significantly reduced from 11.8 mm to 9mm after 3 months and further reduced to 6.6 mm after 6 months of therapy with ormeloxifene (p<0.01). With norethisterone, the mean endometrial thickness was significantly reduced from 11.2 mm to 10mm after 3 months and to 9.2mm 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).

DISCUSSION

Abnormal uterine bleeding accounts for most of the referrals to the Gynaecological clinics. Dysfunctional uterine bleeding (DUB) is a common condition affecting quality of life of many women.[10] Various modes of medical and surgical treatment options are available to treat this condition. The present study was a comparative study to assess the efficacy of ormeloxifene and norethisterone. A total of 100 patients were enrolled in the study, 50 in each group. The women were allotted to 2 groups of 50 each. Group A was given Ormeloxifene tablet 60 mg twice a week for 12 weeks followed by once a week for 12 weeks and group B was given Norethisterone tablet 5 mg twice a day for 21 days followed by 7 days withdrawal for 6 months. Patients were followed up at 3 and 6 months. Haemoglobin concentration and endometrial thickness were measured after 3 and 6 months of the treatment. All patients were in the age group of 40-55 years. Blood loss during menstrual cycles was assessed by means of pictorial blood assessment chart (PBAC). In this study, mean PBAC scores before treatment were 225 in group A and 234 in group B. It was seen that 18% of patients in group A and 26% of patients in group B had PBAC scores of more than 300. At the end of 3 month of treatment mean PBAC scores were 98 and 140 in groups A and B respectively, i.e. it had reduced by 56.8% and 40.1% in groups A and B respectively. The efficacy of treatment was comparable in the two groups. At the end of 6 months, group A showed 66.6% reduction in PBAC score compared to 52.9% reduction in Group B mean PBAC scores being 75 and 110 in both the groups respectively. There was a significant reduction in group A compared to group B. Ormeloxifene competes with estradiol for binding with cytosol receptors. It not only blocks cytosol receptors but also causes their prolonged depletion and has long lasting post withdrawal effect. Ormeloxifene was thus, found to be more effective in reducing menstrual blood loss and controlling DUB compared to cyclical progesterone.

A similar study conducted on 42 women with menorrhagia administering ormeloxifene 60mg twice weekly for 3 months and then once a week for 1 month showed reduction in menorrhagia by 4 months. Shravage et al[11] compared ormeloxifene to another progesterone, medroxyprogesterone acetate. They found an 85.7% reduction in menstrual blood loss with ormeloxifene as compared to 54.76% with medroxyprogesterone acetate.

In this study the mean Hb in group A after treatment was 10.5 gm% and that in group B was 9.9 gm% i.e, more in group A and this was statistically significant. A similar study by Agarwal et al[12] using ormeloxifene reported a statistically significant rise in Hb by 1.8%. In group A 28% of patients had amenorrhoea at the end of 3 months. Another observation was that in group A, passage of clots had reduced by 85.3% at the end of treatment while that in group B had reduced by 40%.

In our study the endometrial thickness before treatment in group A and group B were 11.8 and 11.2 which were comparable. However, at the end of the treatment ormeloxifene was found to cause significant reduction in endometrial thickness by 5.2 mm in group A compared to group B which showed reduction by 3.1 mm. Reduction in endometrial thickness is a definitive objective evidence showing reduction in menstrual blood loss. While both ormeloxifene and norethisterone exhibit antiestrogenic activity in the endometrium preventing endometrial proliferation, ormeloxifene is more efficacious as it directly blocks the oestrogen receptors and thereby prevents mitogenic activity exhibited by oestrogen.

A study conducted by Jacob et al[13] using similar drugs showed reduction in endometrial thickness by both the drugs although the reduction was greater with ormeloxifene compared to norethisterone.

In our study 23% cases in group A failed to respond to medical treatment with ormeloxifene and ended in hysterectomy, 45% cases treated with norethisterone needed surgical management. Failure rate was higher with norethisterone compared to ormeloxifene.

One of the major side effects with ormeloxifene was amenorrhoea. This is due to hypoestrogenic effects causing delay in ovulation thereby lengthening the follicular phase. In majority of the subjects menstrual cyclicity returned to normalcy after 3-6 months. However, in our study patients were in the perimenopausal age group and amenorrhoea was acceptable. Ormeloxifene has been associated with a number of advantages. It can be started at any time during the cycle unlike the progesterones. It is an effective endometrial haemostat controlling bleeding within 48 hours. It is economical compared to any drug. While preventing DUB it also offers perimenopausal bone and cardiovascular protection which is not seen with other drugs.

CONCLUSION

The initial mode of management in DUB is pharmacological therapy. At the end of the study both the groups showed reduction in PBAC score, rise in haemoglobin level and reduction in endometrial thickness. But the effects seen were more in group A treated with ormeloxifene compared to group B treated with norethisterone. Hence, ormeloxifene was found to be superior to norethisterone in the management of DUB. No major side effects were seen with either of the drugs. One of the major limitations of the study was that the 17% of the patients became amenorrhoeic after onset of the treatment, were not followed up later to know whether the menstrual cycles returned to normal or not.

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