Original Research Article

A comparative study on the effectiveness of ormeloxifene versus norethisterone in the management of perimenopausal dysfunctional uterine bleeding

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Abstract

Background: Menstrual disorders are the second most common gynecological condition resulting in hospital referrals. Dysfunctional Uterine Bleeding is defined as abnormal uterine bleeding in the absence of organic disease. Menorrhagia (menstrual blood loss >80 ml per cycle) affects 10-33% of women at some stage in their lives. Approximately 90% of dysfunctional uterine bleeding result from anovulation and 10% occur with ovulatory cycles. Only half of women complaining of heavy menstrual bleeding fit the clinical criteria of more than 80 ml blood loss per cycle. Among women aged 30-49, one in 20 consults her general practitioner each year with menorrhagia. It can be managed both medically and surgically.

Material and methods: Thirty women presenting with DUB were randomly allocated to 2 equal groups, Group-A, which received 60 mg ormeloxifene twice a week for 12 weeks and Group-B, which received 5 mg norethisterone twice daily for 21 days for 3 months. The primary outcome measures were reduction in menstrual blood loss which was measured by fall in PBAC (Pictorial Blood loss Assessment Chart) score, rise in hemoglobin level and reduction in endometrial thickness.

Results: The reduction in mean PBAC score with ormeloxifene (277.33 to 70.11) was significantly more than that seen with norethisterone (246 to 108.5) after 3 months of therapy ($p<0.05$). The increase in hemoglobin level and reduction in endometrial thickness were also found to be significantly more with ormeloxifene than norethisterone (9.68 g% to 11.07 g% vs. 10.17 g% to 10.58 g%, $p<0.05$, and 7.8 mm to 5.3 mm vs. 6.7 mm to 5.9 mm, $p<0.05$, respectively). No major side effects were reported in any group.

Conclusion: Ormeloxifene was found to be more effective than norethisterone in reducing blood loss and reducing endometrial thickness.

Key words

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

Introduction

Menstrual disorders are the second most common gynecological 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]. Approximately 90% of dysfunctional uterine bleeding result from anovulation and 10% occur with ovulatory cycles [4]. Only half of women complaining of heavy menstrual bleeding fit the clinical criteria of more than 80 ml blood loss per cycle [1]. Among women aged 30-49, one in 20 consults her general practitioner each year with menorrhagia [5]. It 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.

Norethisterone is the commonly used progesterone. Progesterone therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss and can be used for both ovulatory as well as anovulatory cycles [1, 6, 7, 8, 9].

Ormeloxifene is a selective estrogen receptor modulator or SERM which is anti-estrogenic on endometrium and breast while estrogenic on bones, vagina, and cardiovascular systems. In a study conducted by Kriplani et al on 42 women receiving ormeloxifene 60 mg biweekly for 3 months followed by once a week for one month showed that 97.7% were relieved of menorrhagia at 4 months [10].

The present study was conducted to compare the efficacy of ormeloxifene with the commonly used progesterones in the treatment of perimenopausal DUB. The progesterone selected for the study was Norethisterone.

Material and methods

This was a comparative study conducted in the Department of Obstetrics and Gynecology, Government medical College, Thrissur, in which 30 women between 40 – 52 years presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause were enrolled. Ethical approval was obtained from the institutional ethical committee. Exclusion criteria were fibroid uterus, adenomyosis, atypical endometrial hyperplasia, pregnancy, bleeding disorders, medical disorders like liver dysfunction, heart disease, migraine, stroke, renal disease, and thyroid dysfunction.

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 included complete blood cell count including hemoglobin (Hb) level, thyroid stimulating hormone, coagulation profile, pap smear, pelvic ultrasound to measure endometrial thickness and rule out any pelvic pathology and endometrial sampling.

The cases were advised to maintain a menstrual diary to record the total number of 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. A PBAC score $\geq$ 100 indicates a

menstrual blood loss ≥ 80 ml and is considered diagnostic for menorrhagia (**Table – 1**) [11].

Table - 1: PBAC scoring [11].

Pads	
Lightly soiled pads	1
Moderately soiled pads	5
Severly soiled pads	20
Clots	
Small clots	1
Large clots	5
Flooding	5

The women were allocated to 2 groups of 15 each. Group A was given Ormeloxifene tablet 60 mg twice 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 3 months. Patients were followed up at 1, 2 and 3 months. During each visit a detailed menstrual history was taken, PBAC score was calculated. Hemoglobin concentration and endometrial thickness were measured after 3 months of the treatment. Any side effects if experienced were also noted.

The primary outcome measures were reduction in amount of menstrual blood loss which was assessed by fall in PBAC score, rise in hemoglobin level and reduction in endometrial thickness done in proliferative phase by a transvaginal ultrasound.

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

Results

All the cases in both the groups were matched well with respect to age, parity, socioeconomic status. The pretreatment mean PBAC score, mean hemoglobin level and mean endometrial thickness were comparable in both the groups.
PBAC scores before treatment were 277.33 and 246 in groups A and B respectively. 20% of patients in group A and 26.66% of patients in group B had PBAC scores of more than 300. Both were comparable. The mean PBAC scores at the end of the study period were 70.11 and 108.55 in groups A and B respectively reporting an overall reduction in MBL by 74.71% and 55.87% in groups A and B respectively (**Table – 2**). Both the groups showed statistically significant fall in PBAC scores following treatment. But the mean reduction in PBAC scores was more in group A which was statistically significant (t=2.316, p=0.028).

The mean Hb was 9.68 and 10.17 in group A and B respectively, before treatment. The two groups were comparable with respect to Hb before treatment. Mean Hb in group A after treatment was 11.07 and that in group B was 10.58 as per **Table - 3**. There was statistically significant increase in hemoglobin following treatment in both the groups. The mean rise in hemoglobin was more in group A than group B and this difference was statistically significant (t=0.42, p<0.001).

The mean endometrial thickness in group A was found to be 7.8 and that of group B was found to be 6.67 as per **Table - 4**. The two values were comparable. Mean endometrial thickness in group A was found to be 5.33 and that of group B was found to be 5.88. There was a statistically significant reduction in endometrial thickness in group receiving Ormeloxifene while that caused by norethisterone was not found to be significant (t=2.4, p=0.023). Subjects with PBAC scores >100 and those who opted for surgical treatment together were taken as failure of treatment. In our study, 20% of patients failed to respond to ormeloxifene and 66.6% of the patients failed to respond to treatment with norethisterone.

Discussion

Dysfunctional uterine bleeding (DUB) is a common condition affecting quality of life of women. Various medical and surgical treatment options have been advocated for this condition. But primary therapy is medical only.

Table - 2: Reduction in PBAC after treatment.

	PBAC before treatment	PBAC after treatment	Mean difference	t	P
Ormeloxifene	277.33	70.11	207.22	12.12	<0.001
Norethisterone	246	108.5	137.4	5.54	<0.001

Table - 3: Rise in Hb following treatment.

	Hb before treatment	Hb after treatment	Mean difference	t	P
Ormeloxifene	9.68	11.07	1.39	11.75	<0.001
Norethisterone	10.17	10.58	0.41	4.157	0.001

Table - 4: Reduction in endometrial thickness.

	ET before treatment	ET after treatment	Mean difference	t	P
Ormeloxifene	7.8	5.3	2.47	4.7	<0.001
Norethisterone	6.7	5.9	0.8	1.7	0.109

The present study was a comparative study to assess the efficacy of ormeloxifene and progesterone i.e., norethisterone. A total of 30 patients were enrolled, 15 in each group. Group A comprised of patients taking ormeloxifene and group B comprised of those taking norethisterone. All patients were in the age group of 40 – 52 years. Parity of patients was comparable in the two groups.

Blood loss during menstrual cycles was assessed by means of pictorial blood assessment chart (PBAC). In this study, PBAC scores before treatment were 277.33 and 246 in groups A and B respectively. It was seen that 20% of patients in group A and 26.66% of patients in group B had PBAC scores of more than 300. At the end of 1 month of treatment mean PBAC scores were 92 and 127.67 in groups A and B respectively, i.e. it had reduced by 66.8% and 48.1% in groups A and B respectively. The efficacy of treatment was comparable in the two groups and there was no statistically significant difference in reduction between the 2 groups. At the end of the 2nd month PBAC scores had reduced by 75.9% and 57.5% from baseline in groups A and B respectively. At the end of 3rd month PBAC score had reduced by 81.3% and 60.5% from the baseline in group A and B 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. Thus efficacy of the drug improves with time which is depicted by increasing reduction in menstrual blood loss with prolonged use.

The mean PBAC scores at the end of the study period were 70.11 and 108.55 in groups A and B respectively reporting an overall reduction in menstrual blood loss (MBL) by 74.71% and 55.87% in groups A and B respectively. Ormeloxifene was thus, found to be more efficacious in reducing menstrual blood loss in DUB compared to cyclical progesterone.

A study conducted in 2004 on 80 subjects using ormeloxifene in a dosage of 60mg twice weekly for 3 months followed by 60 mg weekly for

another 3 months reported a reduction in menorrhagia by at the end of 6 months [8]. 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 at 4 months [10].

The results in our study with respect to efficacy of ormeloxifene in reducing MBL were comparable with majority of the other similar studies. Evidence states that when oral progesterone is given cyclically from D5 – D26 of reduction in MBL is seen [8]. In our study the endometrial thickness before treatment in group A and group B were 7.8 and 6.7 which were comparable. However at the end of the treatment ormeloxifene was found to cause significant reduction in endometrial thickness in group A compared to group B .

Reduction in endometrial thickness is a definitive objective evidence showing reduction in menstrual blood loss.While both ormrloxifene and norethisterone exhibit antiestrogenic activity in the endometrium preventing endometrial proliferation, ormeloxifene is more efficacious as it directly blocks the estrogen receptors and thereby prevents mitogenic activity exhibited by estrogen.

Similar study using ormeloxifene in DUB showed significant reduction in ET after 6 months of treatment [8]. In this study the mean Hb in group A after treatment was 11.07 gm% and that in group B was 10.58 gm% i.e, more in group A and this was statistically significant. A similar study using ormeloxifene reported a statistically significant rise in Hb by 1.3%. In group A 20% of patients had amenorrhoea at the end of 3 months. Another observation was that in group A, passage of clots had reduced by 93.3% at the end of treatment while that in group B had reduced by 40%.

Subjects with PBAC scores >100 and those who opted for surgical treatment together were taken as failure of treatment. In our study, 20% of patients failed to respond to ormeloxifene and 66.6% of the patients failed to respond to treatment with norethisterone.

One of the major side effects of use of ormeloxifene was amenorrhoea. This is due to hypoestrogenic effects causing delay in ovulation thereby lengthening the follicular phase. In various studies conducted, in majority of the subjects menstrual cyclicity returned to normalcy after 3 months. The limitation of our study was lack of follow up after 3 months of study as a result of which it is not possible to comment on whether the menstrual cyclicity returned to normal or not.

Ormeloxifene has been evaluated for management of menorrhagia in various studies since the year 2000. It is associated with a number of advantages. It can be started at any time during the cycle. It is an effective endometrial hemostat controlling bleeding within 48 hours. It is economical compared to any drug. While preventing DUB it is a concurrent contraceptive. It also offers perimenopausal bone and cardiovascular protection which is not seen with any other drug treating DUB.

Conclusion

Dysfunctional uterine bleeding is a common problem that is encountered in the gynecology outpatient department. The main mode of management is pharmacological therapy. Both ormeloxifene and progesterone (norethisterone) were found to be effective in treating these cases as assessed by reduction in PBAC score, rise in hemoglobin level and reduction in endometrial thickness. But the effect was seen more with ormeloxifene. 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 20% of the patients became amenorrhoeic after onset of the treatment were not followed up later to know whether the menstrual cyclicity returned to normal or not. Also, the study was conducted

over a small population over a short duration. Hence, to establish the definitive efficacy of the drug randomized controlled trials with larger subjects over a longer period of time comparing the drug with other medical agents are needed.

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References

1. National Institute for Health and Clinical Excellence. Heavy Menstrual Bleeding. 2007. Available from URL: http://www.nice.org.uk/cg004.
2. Lethaby A, Hickey M, Garry R. Endometrial destruction techniques for heavy menstrual bleeding [Online]. Available from: Cochrane Database of systematic reviews; 2005. Art. No. CD001501.
3. Hallberg L, Hodgahl AM, Nilsson L, Rybo G. Menstrual blood loss - A population study Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand, 1966; 45: 320-51.
4. Frager IS, Jansen RPS, Lobo RA, Whitehead MI. Estrogens and Progestogens in clinical practice. In: Dysfunctional uterine bleeding. Churchill Living Stone Publication, 1998, p. 419-437.
5. Pitkin J. Dysfunctional uterine bleeding. BMJ, 2007; 334(7603): 1110-1.
6. Studd J. Progress in obstetrics and gynecology. In: Current minimal access techniques for dysfunctional uterine bleeding. Churchill Living Stone, 2003; 15: 259-272.
7. National Health Committee. Guidelines for the management of heavy menstrual bleeding. 1998 May, updated in 2001.
8. Lethaby A, Irvine GA, Cameron IT. Cyclical progestogens for heavy menstrual bleeding [Online]. Available from: Cochrane Database of systematic reviews; 2008.
9. Vilos GA, Lefebvre G, Graves GR. SOGC Cinical Practice Guidelines. Guidelines for the management of abnormal uterine bleeding. JOGC, 2001; 106: 1-6.
10. Osborne CK, Zhao H, Fuqua SA. Selective estrogen receptor modulators: structure, function, and clinical use. J Clin Oncol, 2000; 18: 3172-86.
11. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol, 1990; 97: 734-9.