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RESEARCH ARTICLE

COMPARATIVE STUDY BETWEEN ORMELOXIFENE AND NORETHISTERONE IN THE IMPROVEMENT OF MENSTRUAL BLOOD LOSS (MBL) IN ABNORMAL UTERINE BLEEDING

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ABSTRACT

Background: Dysfunctional Uterine Bleeding (DUB) is the most common cause of abnormal uterine bleeding and is a major indication for referral to gynecological clinics. There are many studies comparing the effect of ormeloxifene and progesterone in DUB. The objective of the study was to assess the efficacy in terms of reduction in menstrual bleeding with Ormeloxifene in DUB and compare it with Norethisterone. Subjective improvement was also compared.

Methods: 40 women presenting with DUB were randomly allocated to 2 equal groups, Group-A, which received 60mg ormeloxifene twice a week for 12 weeks followed by 60mg once a week for next 4 weeks and Group-B, which received 5mg norethisterone thrice daily for 21 days for 4 consecutive cycles. The primary outcomes noted were reduction in menstrual blood loss (measured by number of days of bleeding and pads soaked), rise in hemoglobin level and subjective improvement.

Results: The mean days of bleeding during each cycle in cases on ormeloxifene improved by 41.89% in Group A as compared to 28.7% in Group B. The rise in hemoglobin concentration was significantly more with ormeloxifene than norethisterone (5.833g/dl to 6.312g/dl vs 4.500g/dl to 3.388g/dl, $p<0.001$, respectively).

Conclusions: Both Ormeloxifene & Norethisterone are effective in reducing MBL (menstrual blood loss) and hence raising the Hb concentration. Ormeloxifene is more suitable in all age groups with effective therapeutic efficacy and with good compliance of the patient.

INTRODUCTION

Abnormal uterine bleeding is the commonest presenting symptom and major gynecological problem responsible for as many as one-third of all menstruating women at any one time in outpatient gynecologic visit and this proportion crosses the two third threshold in perimenopausal group, overall accounting for 6.2% of genitourinary disease and may account for more than 25% of all hysterectomies.[1,2]

Abnormal uterine bleeding is defined as any bleeding pattern that differs in the frequency, duration and amount from a pattern observed during a normal menstrual cycle.[3]It can result from a broad spectrum of conditions ranging from physiological process to malignant lesions involving organic, systemic and hormonal responses. In a large number of patients, when organic, systemic and pelvic pathology have been ruled out, a diagnosis of dysfunctional uterine bleeding is made. DUB, a diagnosis of exclusion, is one of the most common causes of abnormal uterine bleeding.[4]

Medical management has always been the first therapeutic option to be tried and if it fails to show results, one can resort to surgical interventions.

Hysterectomy should be the last resort in the management of DUB. With the increased concern about the possible long term complications of hysterectomy, more women today prefer effective medical therapy.

Nonsteroidal anti-inflammatory drugs and tranexaemic acid offer a simple therapy which has to be taken during menses, with reductions of 25-35% and 50% respectively in the Menstrual Blood Loss (MBL). Danazol and the gonadatrophin-releasing hormone analogues are highly effective, but their side-effects make them suitable only for a short-term use.

The role of levonorgestrel intrauterine system in menorrhagia is well established and 80% reduction in MBL is seen. It is now considered to be the reference treatment in medical management, but its cost limits its widespread use, especially in developing countries, such as India.

Norethisterone is still the most frequently prescribed drug for dysfunctional uterine bleeding serving 38% of the patient population the reason being cost effectiveness and absence of side effects.[5]

Selective estrogen receptor modulators (SERM) are a new category of therapeutic agents that selectively bind with high

affinity to estrogen receptors (ER) and mimic the effect of estrogen in some tissues but act as estrogen antagonists in others. Ormeloxifene is one of the SERMs (also known as centchroman or Saheli) used primarily as a contraceptive. It mediates its effects by high affinity interaction with ER, antagonizing the effect of estrogen on uterine and breast tissue and stimulating its effect on vagina, bone, cardiovascular system and central nervous system. It is therefore, suitable in the treatment of heavy dysfunctional uterine bleeding (DUB).[6,7]

The aim of this study was to compare the efficacy of Ormeloxifene and Norethisterone in the treatment of AUB in terms of reduction of MBL.

METHODS

In accordance with the ethical principles and with the approval by the institutional ethical review board, this randomized prospective comparative study was conducted in the department of Obstetrics and Gynaecology at Rajah Muthiah Medical College and Hospital from December 2014 till August 2016 for a period of about 2 years.40 women in the age group of 18 and 45 years with complaints of excessive bleeding during menstruation without any organic, systemic or iatrogenic cause were recruited after getting an informed written consent.

The inclusion criteria included women in reproductive age group 18-45 years with excessive menstrual blood loss, absence of coagulopathies, absence of pelvic pathology, not taking any drug affecting menstrual loss, no hormonal therapy in previous 3 months and normal renal function. Women with pathologies such as fibroid, polyp, adnexal mass, postmenopausal women, active bleeding necessitating emergency treatment, hepatic dysfunction, history of malignancy, endocrinopathies, childbirth within one year, abortion within 3 months, IUCD or pill users and congenital anomaly of uterus were excluded from the study.

A detailed history was obtained regarding menstrual, medical, surgical and obstetrical history. General and systemic examination was done. Baseline investigations were conducted for hemoglobin levels. TLC, DLC, bleeding time, clotting time, platelet count, and peripheral smear for cell morphology were done to rule out bleeding dyscrasias. TSH levels were advised to rule out occult hypothyroidism. An ultrasound abdomen and pelvis was done to rule out pelvic pathologies such as fibroid, polyp or adnexal mass.

After the diagnosis of dysfunctional uterine bleeding was made, patients were randomly divided into two groups. Group A received Ormeloxifene (tab. Sevista by torrent pharma) at a dose of 60mg twice weekly (Sunday and Wednesday) for 12 weeks followed by 60mg once weekly (Sunday) for next 4 weeks. Group B received Norethisterone (Tab. Primolut N) at a dose of about 5mg three times a day for 4 consecutive cycles with 7 days gap between two cycles for withdrawal bleed for 6 cycles. The patients were followed at end of 3rd and 4th month of the treatment.

All patients were asked to use sanitary napkin of the same kind, not containing absorbent gel. Participants were taught to maintain a menstrual diary keeping an account of the number of pads used, soakage and passage of clots. Total number of days of bleeding during each menstrual cycle at the end of 3rd and 4th month was asked. Number of pads used on each day was asked and summed up.

Haemoglobin was estimated during follow up. Detailed history regarding number of pads soaked and duration of bleeding in each cycle was recorded. The efficacy was measured was measured in terms of decrease in menstrual blood loss and improvement of haemoglobin. Subjective improvement was asked during each visit.

RESULTS

40 patients were selected for the study. Out of the 40 recruited patients, 6 patients were lost in the follow up (3 opted out for hysterectomy and 3 did not turn up for review). The results of remaining 34 patients are postulated here with respect to blood loss assessment and haemoglobin improvement. There was no significant difference between two groups in age, parity, socioeconomic status, education status, BMI, duration of symptoms, number of pads soaked and duration of each menstrual bleed. The variables used to assess efficacy were also comparable at baseline.

The mean age in our study was 36.525±7.592 years (36.3±6.634 for Group A and 36.75±8.613 for Group B). Majority of cases were married(92.5%), multiparous with live issues of 1-3, educated above primary level, belonged to socioeconomic class III with a mean BMI of 23.15 ±3.776 and the mean duration of symptoms was 20.2± 3.12 months.

Table-1 Demographic profile

Characteristics	Group A Ormeloxifene	Group B Norethisterone	P-Value
Age	36.3000±6.634	36.7500±8.613	0.721
Parity	3.22±1.309	2.88±1.204	0.429
Socio economic status	2.8333±1.04319	3.3125±.70415	0.131
BMI	23.5444±3.61146	23.4500±4.06710	0.941
Duration of symptoms	2.2222±1.06027	2.1250±1.02470	0.788

Table 2 Number of pads soaked per cycle

No. of pads soaked	Group				t	Sig.
	Group- A (Ormeloxifene) (N=18)		Group –B (Norethisterone) (N=16)			
	Mean	SD	Mean	SD		
Pre treatment	31.666	5.246	35.937	4.945	5.922	0.021
End of 3rdmonth	16.666	2.950	21.375	2.895	4.685	<0.001
End of 4th month	10.833	2.121	15.687	3.400	5.055	<0.001

Table 3 Duration of bleeding in each cycle

Duration of bleeding	Group				t	Sig.
	Group- A (Ormeloxifene) (N=18)		Group –B (Norethisterone) (N=16)			
	Mean	SD	Mean	SD		
Pretreatment	5.8333	0.92355	6.3125	0.94648	1.493	0.145
End of 3rd month	4.5000	0.70711	4.7500	0.68313	1.045	0.304
End of 4th month	3.3889	0.60768	4.5000	0.73030	4.841	<0.001

In the present study, the mean days of bleeding during each cycle in cases on ormeloxifene improved from the pretreatment value of about 5.833 ± 0.923 days to 4.5± 0.707 days at the end of 3rd month of treatment to 3.389 ± 0.608 days at the end of 4th month, which shows 41.89% improvement. Whereas in Norethisterone group, it reduced from the pretreatment value of 6.312 ± 0.947 days to 4.75± 0.683 days at the end of 3rd month to 4.50 ± 0.730 days at the end of 4th month, that is a 28.7% improvement. There is improvement in both the groups but it is statistically significant with Ormeloxifene group ($p<0.05$).

At the end of 4th of treatment, patients on Ormeloxifene had a significant reduction of number of pads used during each cycle to 10.833± 2.061 pads from the pretreatment value of 31.667± 5.246 pads signifying a reduction of about 65.8%. Whereas in cases on norethisterone, it was 45 % only (35.937 pads pretreatment to 21.375 pads at the 3rd month to 15.687 pads 4th month). This reduction was also statistically significant (p=0.021).

Table – 4 Average Haemoglobin levels of the two groups

Hb%	Group				t	Sig.
	Group- A (Ormeloxifene) (N=18)		Group –B (Norethisterone) (N=16)			
	Mean	SD	Mean	SD		
Pre treatment	8.5111	0.77299	9.5375	1.15000	3.085	0.004
End of 3rd month	10.0444	0.91602	10.0063	1.12574	0.109	0.914
End of 4th month	11.1222	0.96257	10.2812	0.98198	2.519	0.017

The average haemoglobin level found to be 8.511± 0.773g/dl in the group A at beginning of the study as compared to 9.537 ± 1.15 g/dl in group B. The haemoglobin value changed from 8.511± 0.773g/dl which improved to 10.044± 0.916 g/dl at the end of 3 months (p value =0.914) and 11.122 ±0.963 g/dl at the end of 4 months (p value= 0.017) in case of Group A reflecting an increase by 18.01% at 3rd month and by 30.68 % at end of 4th month. During the same period the rise in haemoglobin in group B was from pretreatment value of 9.537 ± 1.15 g/dl which improved to 10.006±1.126 g/dl at the end of 3rd month and 10.281± 0.982 g/dl at the end of 4th month, which accounts for only 7% improvement.

The difference between the two groups was statistically significant at the end of the treatment. Ormeloxifene was thus better than Norethisterone in terms of rise in amount of haemoglobin.

Table 5 Subjective assessment of improvement

Subjective improvement	Group- A (Ormeloxifene)		Group -B (Norethisterone)		Total	p value
	N	%	N	%	N	
Marked	14	77.8	8	50.0	22	0.239
Mild	3	16.7	6	37.5	9	
No	1	5.6	2	12.5	3	
Worsening	0	0	0	0	0	
Total	18	100.0	16	100.0	34	

77.8% percent of cases showed marked subjective improvement with ormeloxifene as compared to 50% with norethisterone. There was no improvement in 5.6% cases with ormeloxifene as compared to 12.5% with norethisterone. There was no worsening of symptoms in either group.

DISCUSSION

There is no hormonal defect in dysfunctional uterine bleeding; however, disturbances in the endometrial mediators have been noted. A majority of the cases are associated with ovulatory cycles when the cycle control is not an issue, and they can thus be treated with non-hormonal methods such as prostaglandin synthetase inhibitors and antifibrinolytics. Those patients with anovulatory cycles may benefit from an exogenous control of the pattern of bleeding by the use of hormonal preparations.[8]

Medical management has always been the first therapeutic option to be tried and if it fails to show results, one can resort to surgical interventions. A good medical treatment will reduce hysterectomies and associated morbidity and mortality. Hysterectomy should be the last resort in the management of DUB. The RCOG recommends beginning with medical management before resorting to surgical interventions[9]. While hysterectomy offers an effective cure, it is suitable only for those, who have no further wish to conceive. The procedure involves major surgery with significant postoperative morbidity. Endometrial ablation techniques offer an alternative surgical treatment option with significantly reduced postoperative morbidity. They may be unsuitable for women wishing to retain their menstrual or reproductive function and require technical expertise not routinely available.

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 (LNG-IUS) and selective estrogen receptor modulators (SERMS). Despite a decrease in Menstrual Blood Loss (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.

Ormeloxifene is one such SERM which has shown anti-estrogenic effect in the uterus that forms the pharmacological basis of using it in DUB. There was significant improvement on various aspects of menstrual patterns and complaints associated with menorrhagia. Basis for weekly dosing schedule of Ormeloxifene are the long elimination half-life and a long lasting estrogen antagonist action.[10]

The results are comparable with the study done by Grover et al[11] wherein maximum decrease was seen in patients with more pre-treatment bleeding days. Decrease in bleeding days varied from 44 to 149 days per year. Total of bleeding days per year decreased by 71.4% with the treatment as compared to 41.89% in the present study.

In a similar study, Bhattacharyya et al[12] studied 180 cases of DUB, who had completed child bearing and were above 35 years, were randomly assigned to ormeloxifene, progesterone and iron groups. They used similar dose of ormeloxifene with a shorter duration of norethisterone of 10 mg daily for 12 days (from 14th day) in each cycle as compared to 21 days in our study. Iron group was given as 60 mg of elemental iron daily. They also found ormeloxifene to be superior to norethisterone in reducing menstrual blood loss. The increase in hemoglobin concentration occurred maximally with ormeloxifene. There was marked improvement in 81.67% cases on ormeloxifene, which was comparable to 77.8% in the present study, but in only 35% cases on norethisterone, which was much less than our study (50%). They found no improvement in 10% cases on ormeloxifene and 29% on norethisterone as compared to 5.6% and 12.5% in our study.

This study result of 41.8% can be compared with 79.9% as in study by Sweta et al.[13] The mean pretreatment MBL in her study was assessed by pictorial blood chart (PBAC score) and was reduced by 79.9% with treatment. There was a significant reduction in MBL in patients on ormeloxifene (p-value ≤ 0.001). And the rise in the mean hemoglobin level at the end of treatment was1.65g/dl (18.17%). The rise in hemoglobin rise at the end of treatment was significant (p-value ≤ 0.001).

Dhananjay et al[14] studied 35 patients with DUB and found a statistically significant increase in hemoglobin concentration (8.26 to 10.59g/dl, P<0.001) after 3 months of treatment with ormeloxifene.

Kripalani et al[15] studied the efficacy and the safety of ormeloxifene in the management of menorrhagia. It was a pilot study and it was found that Ormeloxifene was an effective and a safe therapeutic option for the medical management of menorrhagia.

Similar to the present study, Neha Agarwal et al[16] found that 22 patients out of 32 had amenorrhoea at end of 4 months of treatment and 90.09% had reduction of menstrual blood loss at the end of 4 months of treatment. 46.6% had significant reduction in number of days of flooding. The mean hemoglobin concentration in group A was improved by 38.29% (7.52gm% to 9.2gm% at 3 months and 10.4 gm% at 6 months, $p<0.01$). Whereas in group B it 14.97% (7.48gm% to 8.4gm% to 8.6 gm%).

Studies by Chitrangada et al[5], Uma gupta et al[17] and Ravibabu et al[18] all have shown similar results indicating Ormeloxifene to be superior to Norethisterone in reducing menstrual blood loss.

Amenorrhoea was a desirable side effect in perimenopausal women on Ormeloxifene. It also has an additive benefit of being protective against breast carcinoma and osteoporosis.
Norethisterone is widely used and studies for detailed assessment of its efficacy and safety in comparison of ormeloxifene are due. If findings of this study are further confirmed ormeloxifene could be used as a first line therapy for dysfunctional uterine bleeding.

CONCLUSION

Majority of the patients presenting with DUB respond well to medical management. Both Ormeloxifene & Norethisterone are effective in reducing MBL, raising the Hb concentration. The results in this study indicate that Ormeloxifene, a non-steroidal, non-hormonal agent, oncologically protective provides effective pharmacological management more than Norethisterone and is suitable for dysfunctional uterine bleeding.

Limitations of the study was that the number of the study group wasless. A larger study group is needed. A long term follow up of the study group was not done.

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