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COMPARATIVE STUDY BETWEEN THE EFFICACY AND SAFETY OF ORMELOXIFENE AND NORETHISTERONE IN THE IN ABNORMAL UTERINE BLEEDING

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A B S T R A C T

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 with respect to reduction in endometrial thickness and safety of Ormeloxifene in DUB and compare it with Norethisterone.

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 endometrial thickness and safety of Ormeloxifene.

Results: The reduction of endometrial thickness was around 42% in group A while it was only 24.6 % in Group B. There was a reduction of 3.111mm (7.394 ± 1.393 mm to 4.283±1.025mm) in Group A and 2.014mm in Group B. The decrease in ET was found to be statistically significant (p-value ≤ 0.001).

Conclusions: Both Ormeloxifene & Norethisterone are effective in reducing ET. Ormeloxifene is more suitable in all age groups with effective therapeutic efficacy and safety 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 tranexamic 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

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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 (with regards to reduction of ET) and safety of Ormeloxifene and Norethisterone in the treatment of AUB.

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. TVS was done to measure endometrial thickness in the proliferative phase.

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. Endometrial thickness was estimated during follow up.

Patients' complaints noted. A track on the compliance was maintained. Note was made on any side effects experienced by them.

The efficacy was measured was measured in terms of decrease in endometrial thickness and safety in terms of side effects experienced by the cases.

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 reduction in ET and side effects. 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

Patient Profile	Group A (Ormeloxifene) n=20	Group B (Norethisterone) n=20	Pvalue
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
Number of pads soaked	31.666±5.246	35.937±4.945	0.021
Duration of bleeding	5.8333±0.92355	6.3125±.94648	0.145
Hb pre treatment	8.5111±.77299	9.5375±1.15000	0.004

Endometrial thickness had a significant reduction of around 42% in group A while it was 24.6 % in Group B. The mean endometrial thickness in the pre-treatment group A was 7.394 ± 1.393 mm. There was decrease in mean ET at 3 months to 5.616±1.299 mm and at 4 months to 4.283±1.025mm. The decrease in ET was found to be statistically significant (p-value ≤ 0.001).In Group B, at end of 4th month it was 6.162 ± 1.325 mm from a pretreatment value of 8.176 ± 1.624 mm.

Table 2 Endometrial thickness reduction

ET	Group				t	Sig.
	Group - A (Ormeloxifene) (N=18)		Group –B (Norethisterone) (N=16)			
	Mean	SD	Mean	SD		
Pretreatment	7.3944	1.39346	8.1769	1.62453	1.512	0.140
End of 3rd month	5.6167	1.29943	6.8188	1.30753	2.685	0.011
End of 4th month	4.2833	1.02513	6.1625	1.32508	4.653	<0.001

Table 3 Side Effects observed for both the groups

Side effects	Group- A (Ormeloxifene)		Group -B (Norethisterone)		Total
	N	%	N	%	
Abdominal pain	1	5.6	2	12.5	3
Amenorrhea	4	22.2	0	0	4
Breakthrough bleeding	0	0	3	18.8	3
Hypomenorrhea	3	16.7	1	6.2	4
Ovarian cyst	2	11.1	0	0	2
Spotting	0	0	3	18.8	3
Vomiting	0	0	3	18.8	3
White discharge	2	11.1	1	6.2	3
Nil	6	33.3	3	18.8	9

33.3% of cases had no side effects with Ormeloxifene. The most common side effects seen with Ormeloxifene was amenorrhoea (22.2%) followed byhypomenorrhoea (16.7%), ovarian cyst (11.1%), white discharge (11.1%) and abdominal pain (5.6%). Amenorrhoea was seen in patients in the age group of 40-45 years. Hence perimenopausal women land up with iatrogenic menopause and hysterectomy is prevented.

In Group B, 18.8% of cases were free of side effects. 37.6 % had breakthrough bleeding and spotting. Few patients had vomiting (18.8%), abdominal pain (12.5%), white discharge (6.2%) and hypomenorrhea (6.2%).

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-oestrogenic 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]

Dhananjay *et al*[11] had the same result where they achieved 41.5% reduction in ET (8.36±2.36 pretreatment to 4.89±1.60mm at the end of 4th month). The mean difference was 3.47mm ($p<0.001$).

Sweta *et al*[12] in their study had a mean endometrial thickness reduction of about 30.87% compared to 42% in the present study. The decrease in ET was found to be statistically significant (p-value ≤ 0.001). 57.15% had no adverse effects with Ormeloxifene with 4 months of treatment. The adverse effects which were observed were mild and included white discharge per vaginum (15.62%), vague abdominal pain (12.5%), gastric upset (6.25%) headache (6.25%) and simple ovarian cyst (3.12%). Amenorrhoea was noted in 22 patients (i.e. 68.75%) in perimenopausal women.

A reduction of 34.9 % was shown by Shagufta *et al*[13] (7.41±2.30mm to 6.82 ± 2.26 mm p value ≤0.05).Bellard Girija *et al*[14] in their study showed a reduction of 31.6% (Pre-treatment 11.4 mm Vs. Post-treatment 7.8 mm). 74 out of 85 subjects (87.05%) showed a reduction in endometrial thickness.

But Chitrangada *et al*[5] in his study has shown a decrease by 18.25% and Neha *et al*[15] (21.9%, p≤0.05). Tapan Kumar *et al*[16], Jayathi *et al*[17] and Uma Gupta[18] *et al* have all shown that Ormeloxifene was superior to Norethisterone in reducing the ET.

Similarly, Kriplani *et al*[19] observed amenorrhoea in 42.9%. In the present study amenorrhoea occurred in majority of patients all of them being of age group 40 years and above and persisted in them as they probably passed into menopause. This finding is similar to study done by Biswas Subhash Chandra *et al*[20] in which amenorrhoea was mostly noted in older (>41 years) age group rather than in younger age group. Thus, the age of the patient significantly affects the occurrence of amenorrhoea with the therapy.

In the present study, occurrence of ovarian cyst was 11.1%. Similar result of 12% was seen in Chitrangada *et al*[5] study. Kriplani *et al*[19] observed ovarian cyst in 7.1% cases. Prasad S observed functional cysts in 22.8% of

patients, which regressed spontaneously. 3.12% cases in the study by Shagufta *et al*[13], 4.35% by Sweta *et al*[12] had ovarian cyst in patients on ormeloxifene.

CONCLUSION

Majority of the patients presenting with DUB respond well to medical management. Both Ormeloxifene & Norethisterone are effective in reducing ET but ormeloxifene is more statistically significant. Ormeloxifene has a good patient acceptability and compliance due to its minimal side effects, low cost and simple dosage schedule. In the peri-menopausal age group, drug is protective against breast malignancy and osteoporosis. Ormeloxifene has the potential to be an effective treatment for DUB and should always be considered amongst the treatment options.

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

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