Ormeloxifene- A new treatment modality in Dysfunctional Uterine Bleeding: efficacy and safety

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Abstract

Background/ Objective: To compare the efficacy and safety of ormeloxifene and norethisterone in the medical management of Dysfunctional Uterine Bleeding (DUB).

Methods: 100 cases of DUB aged between 30 to 50years, who have completed child bearing, were randomly assigned ormeloxifene and Norethisterone groups. Ormeloxifene group received ormeloxifene 60 mg twice a week for 12 weeks and then once a week for next 12 weeks. Norethisterone group received norethisterone 5 mg twice daily for 21 days in every cycle for six cycles. Patients were followed up at end of 3rd and 6th month of therapy, and then at the end of 3rd month after treatment were stopped. The treatment with ormeloxifene and Norethisterone was evaluated by measuring the menstrual blood loss (MBL) by a pictorial blood loss assessment chart (PBAC), Hb g/dl and the endometrial thickness before and after 3 months of treatment. The side effects and patient acceptability of drug ormeloxifene were compared with norethisterone.

Results: The mean PBAC score and Endometrial thickness (ET) in Norethisterone group and ormeloxifen group reduced significantly (*P*-value <0.0001) at the end of 3rd month after treatment were stopped. The Hb level increased maximum in Ormeloxifen group followed by Norethisterone group significantly (p<0.0001). In Norethisterone group side effects were hypomenorrhoea, spotting and breakthrough bleeding. In Ormeloxifen group side effects were amenorrhoea, hypomenorrhoea, spotting, Utero-vaginal prolapse.

Conclusion: Ormeloxifene is more effective and safe therapeutic option as compared to Norethisterone for the medical management of DUB.

Keywords: DUB (Dysfunctional uterine bleeding), MBL (menstrual blood loss), PBAC (pictorial blood loss assessment chart), Hb (haemoglobin), ET (Endometrial thickness).

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Introduction

Menstrual dysfunction, comparable other aspects of sexual and reproductive health, is not incorporated in the Global Burden of Disease estimates[1,2] and, even as reproductive health programs expand their focus to report gynaecologic morbidity, the utility of evaluating and treating menstrual problems is not usually considered[3]. DUB interferes with a woman's physical, emotional, social, and material quality of life in her reproductive age. Menstrual bleeding has significant economic implications for women in the workplace[4]. Though the results of surgical options appear more promising, one cannot deny the morbidity associated with these options. In recent years women unwilling to accept surgical intervention in availability of an effective medical therapy. Nonsteroidal anti-inflammatory drugs, antifibrinolytics, progesterones, danazol, levonorgestrel releasing intrauterine system, gonadotropin releasing hormone analogues have all been used with variable outcomes. Progestins still considered as gold standard and are effective in the treatment of ovulatory type of DUB[5]. In a search of better management options for DUB, Ormeloxifene came with promising outcome, however needs more clinical trials. Ormeloxifene is one of the selective estrogen receptor modulators, which acts on the estrogen receptor, causing the endometrium to grow more slowly.

Methods

The prospective analytical multicentre study was carried out on randomly selected patients obtained from outpatient department of Obstetrics and Gynaecology from 1st September 2011 to 31st August 2013 (2 years). The patients were diagnosed cases of DUB. 100 cases of DUB aged between 30 to 50 years, who have completed child bearing, were randomly assigned ormeloxifene and Norethisterone groups. An informed consent was obtained from the patients who were selected for the study. All the patients were admitted and the causes for the abnormal uterine bleeding were ruled out by taking the history, by doing a clinical examination and by doing investigations like complete blood count, coagulation profile, liver function test, thyroid profile, ultrasonography of the pelvis, Pap

smear and endometrial biopsy. Those with history of abortion within 3 months, or child birth within 1 year were excluded. Likewise IUCD or oral contraceptive pill users or those with diabetes mellitus or congenital anomaly of uterus were also excluded. Ormeloxifene group received ormeloxifene 60 mg twice a week for 12 weeks and then once a week for next 12 weeks. Norethisterone group received norethisterone 5 mg twice daily for 21 days from day 5th to day 25th in every cycle for six cycles. Patients were followed up at 3 and 6 months of therapy, then at 3 months after treatment were stopped. 18 patients in the ormeloxifene group and 31 patients in the Norethisterone group were opted out of the study. Fresh 49 cases were recruited into these groups among which shortfall of 18 patients in the ormeloxifene group and shortfall of 31 patients in the Norethisterone group were achieved to have uniform group of patients (50 each) for both the medicines. Further non- reporting of patients for the study not observed.

The treatment with ormeloxifene and Norethisterone was evaluated by measuring the menstrual blood loss (MBL) by a pictorial blood loss assessment chart (PBAC), Hb g/dl and the endometrial thickness before starting the treatment and 3months after completion of treatment.

A PBAC score of greater than or equal to 100 was considered diagnostic of menorrhagia.

Endometrial thickness (ET) was measured in proliferative phase using transvaginal sonography and haemoglobin (Hb) level was measured before starting the treatment and 3months after completion of treatment. The side effects and patient acceptability of drug ormeloxifene were compared with norethisterone.

Results

Pictoral Blood Assessment Chart Score(PBAC): Pre-treatment and post treatment values differed with statistical significance ($p<0.0001$) in both groups. PBAC score reduced after the drug administration in both groups and the PBAC scores reduced significantly in the Ormeloxifen group followed by Norethisterone group (Table 1).

Endometrial Thickness (ET): Analysis of endometrial thickness showed that the pre and post treatment values differed significantly ($p<0.0001$) in both Norethisterone group and Ormeloxifen group. It is reduced after the drug administration maximally in Ormeloxifen group followed by Norethisterone group (Table 1).

Haemoglobin level (Hb): From the analysis, it is reflected that the pre and post treatment values differed significantly ($p<0.0001$) in both Norethisterone group and Ormeloxifen group. The Hb level increased maximum in Ormeloxifen group followed by Norethisterone group (Table 1).

Complications: In Norethisterone group side effects were hypomenorrhoea in 1 patient, spotting in 6 patients and breakthrough bleeding in 1 patient. In Ormeloxifen group 14 patients developed amenorrhoea, 6 hypomenorrhoea, 2 spotting, 1 Utero-vaginal prolapsed and amenorrhoea. These complications were rather beneficial in these patients except breakthrough bleeding and UV prolapse (Table 2).

Table 1

Group	No.	Variable	Minimum	Maximum	Mean	Standard deviation	P value
Norethisterone' group	50	PBAC (Pre)	120	320	190.08	47.6897641	t = 14.71499 p<0.0001
Norethisterone' group	50	PBAC (Post)	20	130	92	17.13760777	
'Ormeloxifene' group	50	PBAC (Pre)	160	400	227.36	41.078832	t = 24.44622 p<0.0001
'Ormeloxifene' group	50	PBAC (Post)	0	130	62	31.31261727	
Norethisterone' group	50	ET (Pre)	7	15	8.652	1.199873	t = 9.551551 p<0.0001
Norethisterone' group	50	ET (Post)	4	9	6.84	1.18	
'Ormeloxifene' group	50	ET (Pre)	8	14.8	9.332	1.11482	t = 19.23275 p<0.0001
'Ormeloxifene' group	50	ET (Post)	2	9	5.232	1.4163954	
Norethisterone' group	50	Hb (pre)	7	11	8.322	0.927424	t = 9.0764 p<0.0001
Norethisterone'	50	Hb (Post)	8	12	10.17	0.8789198	

group							
'Ormeloxifene' group	50	Hb (pre)	7.2	10.8	8.23	0.8273452	t = 20.0609 p<0.0001
'Ormeloxifene' group	50	Hb (Post)	9.2	13	11.668	0.9731269	

Table 2: Complications among 'Norethisterone' and 'Ormeloxifene' group

Complications	'Norethisterone' group	Percentage(%)	'Ormeloxifene' group	Percentage(%)
Amenorrhoea	-	-	14	
Hypomenorrhoea	1		6	
Spotting	6		2	
Breakthrough bleeding	1			
Utero-vaginal prolapsed and amenorrhoea			1	
Treatment failure	34%		10%	
Total		100		100

Discussion

The aim of management of DUB is to control bleeding and ensure general well-being as well as to improve quality of life. Ormeloxifen was certainly superior as compared to Norethisterone. Results in Norethisterone group are in agreement to the findings of Fraser, 1990[6] and Irvine et al 1998[7].

Clinical trials on the use of ormeloxifen in DUB are limited. A study by Biswas et al in 2004[8] showed similar outcome in ormeloxifen group. Our findings with respect to PBAC score were accordance with the study done by Kriplani A. et al[9]. The results of our study were comparable with studies conducted by Bhattacharyya TK et al[10] and Jyotsna Shravage et al[11].

The adverse effect of genital prolapsed in 1 patient with ormeloxifen group. Similar side effects were also noticed by Goldstein et al[12] and Bhattacharyya TK et al[10]. More clinical trials are required to validate these side effects. Apart from these side effects ormeloxifen has been found to have a favourable effect compared to norethisterone.

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