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Original Research Article

Comparison between Ormeloxifene and Norethisterone in reducing menorrhagia in dysfunctional uterine bleeding

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ABSTRACT

Background: Dysfunctional Uterine Bleeding (DUB) is a condition that affects nearly every woman at some point in her life. This study aims to compare the efficacy of Ormeloxifene and Norethisterone in reducing menorrhagia in such patients.

Methods: This prospective study was done on 100 women presenting with dysfunctional uterine bleeding, of 20-50 years of age, who were ready for follow-up and were allocated into two equal groups, one was given Ormeloxifene and the other was given Norethisterone for a period of 3 months. Haemoglobin levels, endometrial thickness on ultrasound and Pictorial Blood loss Assessment Chart (PBAC) scores were assessed before and after the treatment.

Results: It was found that both Ormeloxifene and Norethisterone reduced menorrhagia, with a significant difference in PBAC scores (p value <0.05). There was a notable reduction in PBAC scores in Ormeloxifene group (66.53% change from pretreatment mean value) as compared to Norethisterone group (31.38% change from pretreatment mean value); and same holds true for the change in haemoglobin levels as well as endometrial thickness. Ormeloxifene was found to have a greater effect on heavy menstrual bleeding in comparison to Norethisterone.

Conclusions: Ormeloxifene is a new modality and is found to be a better option in reducing menorrhagia in DUB in respect to a greater success rate, better compliance and cost effectiveness.

Keywords: Endometrial thickness, Dysfunctional uterine bleeding, Norethisterone, Ormeloxifene, PBAC score

INTRODUCTION

Dysfunctional Uterine Bleeding (DUB) is defined as a state of abnormal uterine bleeding without any clinically detectable organic pelvic pathology like tumor, inflammation or pregnancy and is a diagnosis of exclusion.

It is the most common cause of abnormal vaginal bleeding during a woman's reproductive years.¹

The treatment options for dysfunctional uterine bleeding are diverse, which can be finally tailored to cater the needs of patients of different socioeconomic background, different age groups and different reproductive needs.²

Treatment options range from offering medical measures such as cyclooxygenase inhibitors, tranexamic acid, hormonal agents and in cases not managed by medical therapy offering surgical management.³

Ormeloxifene (also known as Centchroman) is one of the selective estrogen receptor modulators. It is a non-steroidal, non-hormonal oral contraceptive which is taken once a week.⁴ In India, Ormeloxifene has been available as a birth control product since the early 1990s.

It is developed as Centchroman by Indian Central Drug Research Institute, Lucknow, India and it is currently marketed here under the trade name, Saheli.⁵ It mediates its effects by high affinity interaction with estrogen

receptors, antagonizing the effect of estrogen on uterine and breast tissue and stimulating effect on vagina, bone, cardiovascular system and central nervous system.⁶ Norethisterone (a conventional progesterone) is 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.

It suppresses endometrial development, re-establish predictable bleeding patterns, decrease menstrual flow and lower the risk of iron deficiency anaemia.⁷

METHODS

In the present study, patients presenting with dysfunctional uterine bleeding (DUB) to the Department of Obstetrics and Gynaecology, Sardar Patel Medical College, Bikaner, Rajasthan (India) during the specified period from September 2015 to August 2016 were taken up for study.

This was a comparative prospective study conducted in which 100 women between 20-50 years presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause were enrolled.

Inclusion criteria

- All patients with DUB of 20-50 years of age were included in the study.
- All patients who were ready for follow up.

Exclusion criteria

- Patients who were pregnant, lactating, with history of heart disease, hypertension, migraine, polycystic ovarian disease, liver and kidney impairment and thyroid dysfunction were excluded.
- Also, patients with fibroid uterus, adenomyosis, atypical endometrial hyperplasia, bleeding disorders were also excluded.

Informed consent was taken from all the patients. After obtaining an approval from institutional ethics committee, 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 haemoglobin (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 ≥ 100 indicates a menstrual blood loss ≥ 80 ml and is considered diagnostic for menorrhagia.⁸

The women were allocated into 2 groups, and cases were taken until each group had 50 cases, who were ready for follow-up. 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 3 months.

During each visit a detailed menstrual history was taken, PBAC score was calculated. Haemoglobin level 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 an ultrasound.

All outcome measuring parameters were presented as Mean and were analyzed using the Z technique. Statistical significance was taken as $p \leq 0.05$.

RESULTS

Table 1 shows analysis of age distribution. 50% of cases in Group A and 48% in Group B belonged to age group between 31-40 years, with mean age of 37.90 years in Group A and 35.40 years in Group B. The two groups were comparable to each other.

Majority (94%) of the patients were multiparae. In Group A, 46% of patients had 4 or more children and in Group B, 32% had 3 and 32% had 2 children.

Both the groups were comparable to each other. Most of the patients belonged to rural population, with 56% in Group A and 62% in Group B.

With regard to distribution of patients according to duration of symptoms, most of the patients had 4-6 months of duration of symptoms (34% in Group A and 36% in Group B). Mean duration of symptoms in Group A was 6.8 months and in Group B was 6.7 months. Mean haemoglobin level in Group A was 7.3gm% and in Group B was 7.5gm%. Most of the patients had endometrial thickness in the range of 10.1 to 15mm (64% in Group A and 76% in group B).

Table 1: Distribution of variables among study subjects.

Variables	Drug A group (Ormeloxifene)		Drug B group (Norethiesterone)	
	No.	%	No.	%
Distribution of patients according to age (in years)				
20-30	9	18	17	34
31-40	25	50	24	48
41-50	16	32	9	18
Total	50	100	50	100
Distribution of patients according to parity				
1	1	2	5	10
2	12	24	16	32
3	14	28	16	32
>=4	23	46	13	26
Total	50	100	50	100
Distribution of patients according to residence				
Urban	22	44	19	38
Rural	28	56	31	62
Total	50	100	50	100
Distribution of patients according to duration of symptoms (in months)				
0-3	11	22	10	20
4-6	17	34	18	36
7-9	12	24	11	22
10-12	9	18	10	20
>12	1	2	1	2
Total	50	100	50	100
Hemoglobin (gm%) level of patients prior to treatment				
<6	3	6	2	4
6-8	36	72	35	70
8.1-10	11	22	13	26
Total	50	100	50	100
Endometrial thickness (mm) on USG prior to treatment				
0-5	1	2	0	0
5.1-10	12	24	10	20
10.1-15	32	64	38	76
15.1-20	5	10	2	4
Total	50	100	50	100
PBAC score prior to treatment				
100-200	3	6	0	0
201-300	33	66	39	78
301-400	14	28	11	22
Total	50	100	50	100

Table 2: Mean of baseline characteristics of patients.

Baseline characteristics	Drug A (Ormeloxifene)	Drug B (Norethisterone)	p-value
	Mean	Mean	
Age (years)	37.90	35.40	-
Parity	3.40	2.80	-
Duration of symptoms (months)	6.86	6.76	0.872
Haemoglobin (gm%)	7.30	7.5	0.397
Endometrial thickness (mm)	11.9	11.7	0.709
PBAC score	274	274	0.942

Mean PBAC score in both the groups was 274 with most of the patients in the range of 201-300 (66% in Group A

and 78% in group B) (Table 2). Table 3 shows the comparison in between Drug A and Drug B in respect to

pre- and post-treatment values of mean PBAC score, mean haemoglobin concentration and mean endometrial

thickness, and all these were found to be significant in both the groups (p value <0.05).

Table 3: Comparison between pre- and post-treatment values of different parameters.

Group	Pre-treatment	After 3 months of treatment	p-value
Mean PBAC score			
Drug A group (Ormeloxifene)	274	91.7	0.0004
Drug B group (Norethisterone)	274	188	0.0009
Mean Hb (gm%)			
Drug A group (Ormeloxifene)	7.3	9.6	0.0006
Drug B group (Norethisterone)	7.5	8.5	0.0008
Mean endometrial thickness (mm)			
Drug A group (Ormeloxifene)	11.9	7.9	0.0003
Drug B group (Norethisterone)	11.7	10.3	0.0006

It also shows change in PBAC score after 3 months of treatment, with percentage change of 66.53% in Group A and 31.38% in Group B.

The percentage change in haemoglobin was of 31.5% in Group A and of 13.3% in Group B; and the percentage change in endometrial thickness of 25.2% in Group A and of 11.9% in Group B, which was all significant (p value <0.05).

Table (04) shows the side effects of the given treatment, which were mild, and they didn't affect the compliance of the patients receiving the treatment.

Table 4: Side effects of treatment.

Side effects	Drug A group (Ormeloxifene)		Drug B group (Norethisterone)	
	No.	%	No.	%
Nausea	7	14	10	20
Headache	3	6	3	6
White discharge	6	12	2	4
Spotting	-	-	5	10
Total	13	26	16	32
p-value	0.972			

Most common side effect in both the groups was nausea. 26% of patients in Group A had side effects out of which 14% had nausea and in Group B, 32% patients had side effects out of which 20% had nausea.

Side effects are slightly more in Group B, but the p value was not significant. Table (05) shows the comparison of both the drugs by their market price.

The cost of one tablet of ormeloxifene is Rs.9 and that of norethisterone is Rs.4, so the total cost of 3 months of treatment with Drug A would be Rs.216 and that with Drug B would be Rs.504, which is almost twice that of

Drug A, thereby making Drug A more cost effective in comparison to Drug B.

Table 5: Comparison of both drugs by market price.

Market price (in Rupees)	Drug A (Ormeloxifene)	Drug B (Norethisterone)
Cost of one tablet	9	4
Cost of drug for 3 months of treatment	216	504

DISCUSSION

Dysfunctional uterine bleeding (DUB) is a common problem seen in women of reproductive age group.

The mean age of the patients was 37.90 years in Group A and 35.40 years in Group B. This study group is also comparable with previous studies.⁹⁻¹¹

The reason could be that in younger years of the reproductive life, the heavy menstrual bleeding might not cause much of a trouble to the affected women as most of the times the bleeding is temporarily halted during the pregnancies and the health status of young women is mostly better than the women in their later years of life, so they usually present late to the hospital.

Most of the patients were multiparae, which was also comparable to the previous studies.⁹⁻¹¹

The duration of symptoms was high as seen in previous studies also, the reason could be that these women are usually neglected, so they present late to the hospital.^{9,11}

There was decrement in PBAC score in both the groups after 3 months of treatment, with percentage change in PBAC score of 66.53% in Group A and of 31.38% in Group B (Figure 01).

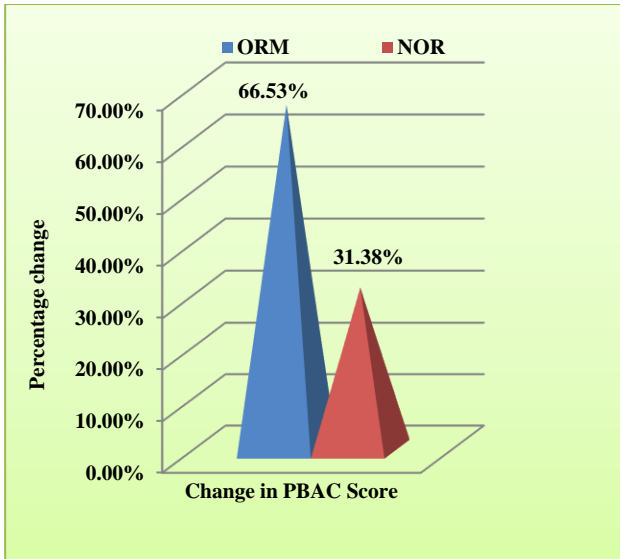


Figure 1: Percentage change in PBAC score after treatment.

The haemoglobin levels increased significantly in these patients after 3 months of treatment, with percentage change in haemoglobin of 31.5% in Group A and of 13.3% in Group B (Figure 02).

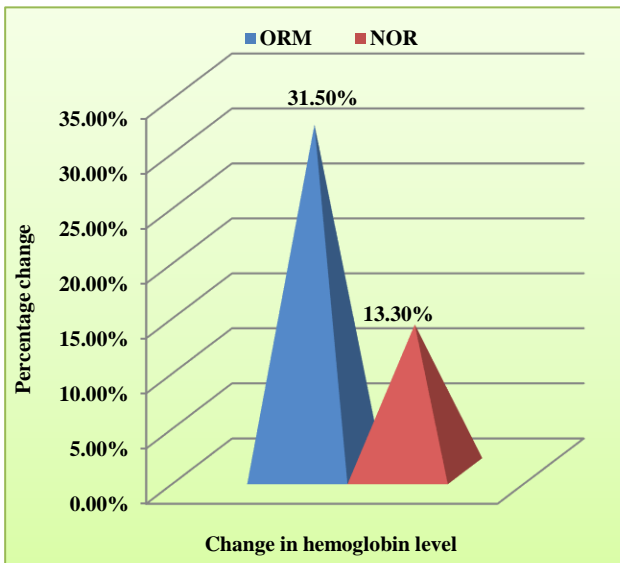


Figure 2: Percentage change in haemoglobin levels after treatment.

The endometrial thickness on ultrasonography decreased after 3 months of treatment, with percentage change in thickness of 25.2% in Group A and of 11.9% in Group B (Figure 03). All of which was significant (p value <0.05) and similar to previously conducted studies.^{9,10,12,13} This shows a decrement in the amount of menstrual blood loss over the course of treatment. PBAC score is not routinely used to assess the menstrual blood loss in patients attending the hospitals, but it should be considered for this purpose. As seen in present study, PBAC score

directly correlates to the haemoglobin levels in patients where the cause of anaemia was only heavy menstrual blood loss. PBAC score can help in subjective quantification of blood loss during each cycle and can be used as a helpful guide in patients requiring some kind of intervention, even before the development of anaemia and before any significant effect on their quality of life.

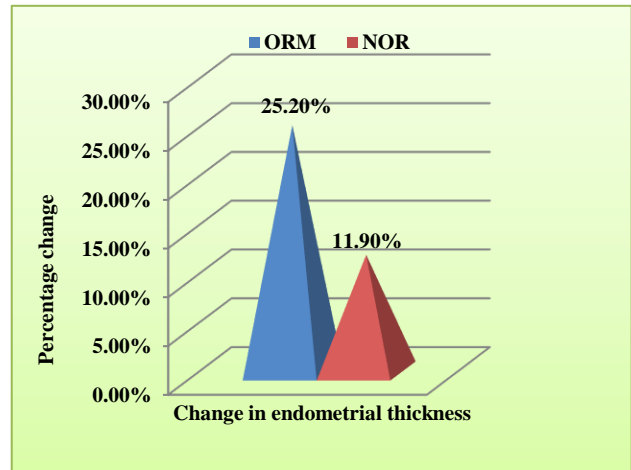


Figure 3: Percentage change in endometrial thickness after treatment.

The PBAC scores, if mentioned, in previous records can be very helpful for comparison and quantification of blood loss. There were few minor side effects in both the treatment groups which did not cause any failure of compliance. Ormeloxifene is more cost effective in comparison to conventional progesterone. On comparison with Norethisterone (a conventional progesterone), in present study, we found Ormeloxifene to be a better option in respect to a greater success rate, better compliance and cost effectiveness.

CONCLUSION

Dysfunctional Uterine Bleeding (DUB) is considered to be caused because of the hormonal imbalance, eventually leading to hyperestrogenic state, which can be quite successfully treated by the medical management, like conventional progestins or Selective Estrogen Receptor Modulators.

The ideal therapy to treat DUB should be a designer drug which can block the action of estrogen on the endometrium, but not its beneficial actions in the body.

PBAC score is a simple tool for assessment of menstrual blood loss. It is quite cost effective as it requires no special equipment's or setup and is less time consuming also. With this score, we can easily differentiate women having normal blood flow during menses from those having heavy menstrual bleeding. It can be helpful in quantifying, comparing and documenting the amount of bleeding during each cycle, and also to see the efficacy of the treatment in patients of abnormal uterine bleeding.

So, this score should be routinely used in patients complaining of heavy menstrual bleeding.

However, present study is on a small scale and is of short duration and larger multicentric studies and trials are required to recommend Ormeloxifene as an ideal regime for the treatment of dysfunctional uterine bleeding.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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