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Ormeloxifene versus oral contraceptive pills in the management of DUB

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Abstract
Background: DUB is defined as abnormal uterine bleeding without any clinically detectable pelvic pathology. The present study was conducted to compare the efficacy and safety of ormeloxifene and combined oral contraceptive pills in medical management of DUB.
Methods: 110 cases of DUB aged between 25 and 45 years were randomly assigned into two groups. Group A received Ormeloxifene 60mg twice a week for 3 months and then once a week for next 3 months. Group B received combined oral contraceptive pills (Levonorgestrel 0.15mg and Ethinylestradiol 20mcg) one tablet from the 5th day of menses for 21 days given for 6 cycles. Regular follow up was done to assess response, compliance and side effects of drug. The treatment was evaluated by measuring menstrual blood loss by PBAC (Pictoral Blood Loss Assessment Chart), Haemoglobin g/dl and endometrial thickness before and after treatment.
Results: Ormeloxifene was found to be significantly more effective ($P< 0.0001$) than OC pills in controlling menorrhagia. There was significant decrease in endometrial thickness and improvement in Haemoglobin level in ormeloxifene group.
Conclusion: Ormeloxifene is more effective and well tolerated than OC pills in treatment of DUB.

Keywords: Ormeloxifene, dysfunctional uterine bleeding, oral contraceptive pills

Introduction

Dysfunctional Uterine Bleeding (DUB) is an irregular uterine bleeding in absence of any organic, systemic or iatrogenic cause [1]. It is a major cause for referral to gynecological outpatient clinics and account for one of the common indications for hysterectomy globally with added risk of surgical and anaesthetic complications [2]. Women with DUB who wish to retain fertility, medical management has always been the first therapeutic option to be tried [3]. The option for initial management of DUB include NSAIDs, antifibrinolytics, progesterone, combined oral contraceptive pills, Danazol and GnRH analogues. Selective Estrogen Receptor Modulators (SERM) are well known as designer estrogens as it has high affinity towards estrogen receptors and mimic the effect of estrogen in some tissues but as antagonist in others [4]. Ormeloxifene is one of the selective estrogen receptor modulators which act on estrogen receptors (ER) in all tissues [5]. The normal menstrual cycle comprises of cyclic, orderly sloughing of uterine lining at the interval of 21-35 days, the flow lasting 2-6 days and a blood loss of 80ml [6].
Ormeloxifene is very effective in reducing upto 77-85% blood loss with minimal side effects and causes amenorrhea in 17-42% patients [7]. It normalizes the bleeding from uterine cavity by regularizing the expression of estrogen receptors on the endometrium [8].

Methods

In accordance with the ethical principles and with the approval by the institutional ethical committee, this prospective comparative study was conducted in Department of Obstetrics and Gynaecology at Kampala Vinayaga Institute of Medical Sciences and Research Centre from December 2018 till December 2019 for a period of about one year. After getting informed and written consent, 110 women in the age group of 25 and 45 years with the history of excessive bleeding during menstruation without any systemic, organic or iatrogenic cause were recruited for the study. Haemoglobin level, coagulation profile and thyroid profile was checked for all patients. Transvaginal ultrasound was done from each patient and endometrial biopsy was taken if necessary. Patients were randomly divided into two groups.

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Group A received Ormeloxifene at a dose of 60mg twice weekly for 3 months followed by 60mg once weekly for next 3 months. Group B were given combined oral contraceptive pills containing 20 mcg ethinyl estradiol and 0.15mg levonorgestrel from 5th day of menses for 6 cycles.

Patients were advised to use same kind of sanitary napkins and maintain menstrual calendar, number of pads used, number of days bleeding occurred, size of passage of clots. Total number of days during each menstrual cycle at the end of 6th month was asked. Objective assessment of blood loss was obtained by using Pictorial Blood Assessment Chart. A PBAC score >100 indicates menorrhagia. The parameters used to compare were mean menstrual blood loss, endometrial thickness measured by transvaginal ultrasound and mean haemoglobin concentration. Patients were interviewed for compliance with drug, side effects of drug and effect on quality of life after each month and at the trial period of 6 months.

Statistical Methods

PBAC score, HB level, endometrial thickness (mm) were considered as primary outcome variables. Study group (A Vs B) was considered as Primary explanatory variable. Demographic variables like age, marital status, socio economic status and parity, duration of menorrhagia were considered as other study relevant variables.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagram, pie diagram.

All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution For normally distributed Quantitative parameters the mean values were compared between study groups using Independent sample t-test (2 groups). For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups).

Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test (If the overall sample size was <20 or if the expected number in any one of the cells is <5, Fisher's exact test was used.)

P value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis [1].

1. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

A total of 110 subjects were included in the final analysis.

Table 1: Descriptive analysis of study group in the study population (N=110)

Study group	Frequency	Percentages
Group A	55	50.00%
Group B	55	50.00%

Among the study population, 55 (50%) were group A and 55 (50%) were group B. (Table 1 & figure 1)
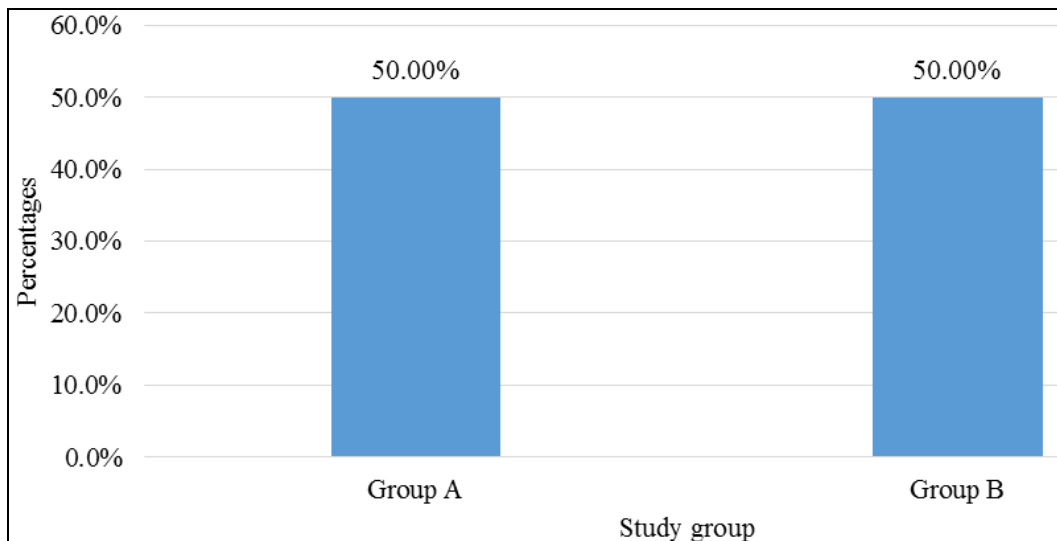

Fig 1: Bar chart of study group in the study population (N=110)

Table 2: Comparison of baseline characteristics between the study groups (N=110)

Parameters	Study group		P-value
	Group A (N=55)	Group B (N=55)	
Age (Mean± SD)	38.15 ± 3.4	37.31 ± 4.19	0.253
Marital status			
Married	48 (87.27%)	43 (78.18%)	0.207
Unmarried	7 (12.72%)	12 (21.81%)	0.207
Parity			
P1L1	12 (21.81%)	4 (7.272%)	0.081
P2L2	35 (63.63%)	39 (70.90%)	0.081
Nulliparous	8 (14.54%)	12 (21.81%)	0.081
Socio economic class			

II	5 (9.090%)	0 (0%)	**
III	26 (47.27%)	25 (45.45%)	
IV	23 (41.81%)	30 (54.54%)	
V	1 (1.818%)	0 (0%)	
Duration of menorrhagia in days			
Duration of menorrhagia in days (Mean± SD)	8.33 ± 1.39	8.36 ± 1.06	0.878

*No statistical test was applied- due to 0 subjects in the cells

The mean age was 38.15 ± 3.4 years in group A and it was 37.31 ± 4.19 years in group B and the mean difference was statistically not significant (P value 0.253). Among the group A, 48 (87.27%) were married and 7 (12.72%) were unmarried. Among the group B, 43 (78.18%) were married and 12 (21.81%) were unmarried. The difference in the proportion of marital status between study groups was statistically not significant (P value 0.207). Among the group A, 12 (21.81%) had P1L1 and 35 (63.63%) had P2L2. Among the group B, 4 (7.272%) had P1L1 and 39 (70.90%) had P2L2. The difference in the proportion of parity between study groups was statistically not significant (P value 0.081). Among the group A, 5 (9.090%) were with socio economic class II, 26 (47.27%) were with socio economic class III, 23 (41.81%) socio economic class IV and 1 (1.818%) was socio economic class V. Among the group B, 25 (45.45%) were with socio economic class III and 30 (54.54%) socio economic class IV. The mean duration of menorrhagia was 8.33 ± 1.39 days in group A and it was 8.36 ± 1.06 in group B and the difference was statistically not significant (P value 0.878). (Table 2)

Table 3: Comparison of clinical parameters between the two groups at different follow-up time periods (N=110)

Parameter	Group A Median (IQR)	Group B Median (IQR)	Mann Whitney U test (P value)
Cycle length in days	30 (26,32)	28 (26,32)	0.076
PBAC score pre-Rx	220 (215,236)	223 (216,236)	0.827
PBAC score after Rx	86 (67,90)	160 (146,170)	<0.001
HB level (g/dl) pre-Rx	8.2 (7.6,8.5)	8.4 (7.9,8.8)	0.029
HB level (g/dl) after Rx	10.7 (10.5,11.1)	9.4 (8.8,9.8)	<0.001

Among the group A, the median cycle length was 30 days (IQR 26 to 32) and it was 28 days (IQR26 to 32) in group B, the difference in the cycle length between study group was statistically not significant (P value 0.076). Among the group A, the median PBAC score pre Rx was 220 (IQR 215 to 236) and it was 223 (IQR 216 to 236) in group B, the difference in the cycle length between study group was statistically not significant (P value 0.827). Among the group A, the median PBAC score after Rx was 86 (IQR 67 to 90) and it was 160 (IQR 146 to 170) in group B. Among the group A, the median HB level pre Rx was 8.2 g/dl (IQR 7.6 to 8.5) and it was 8.4 g/dl (IQR 7.9 to 8.8) in group B. Among the group A, the median HB level after Rx was 10.7 g/dl (IQR 10.5 to 11.1) and it was 9.4 g/dl (IQR 8.8 to 9.8) in group B. the difference in the PBAC and HB level between study group was statistically significant (P value <0.05). (Table 3)

Table 4: Comparison of mean of endometrial thickness between the study groups (N=110)

Endometrial thickness (mm)	Study group (Mean± SD)		P value
	Group A (N=55)	Group B (N=55)	
Pre Rx	11.13 ± 1.13	11.21 ± 0.92	0.679
After Rx	8.21 ± 0.91	9.11 ± 0.81	<0.001

The mean endometrial thickness pre rx was 11.13 ± 1.13 mm in group A and it was 11.21 ± 0.92mm in group B, the mean difference was statistically not significant (P value 0.679). The mean endometrial thickness after rx was 8.21 ± 0.91 mm in group A and it was 9.11 ± 0.81 mm in group B, the mean difference was statistically significant (P value <0.001). (Table 4)

Table 5: Comparison of mean of clinical parameters mean difference between the study groups (N=110)

Parameter	Study group (Mean± SD)		P value
	Group A (N=55)	Group B (N=55)	
PBAC score difference	143.49 ± 19.94	71.33 ± 28.97	<0.001
HB difference	2.63 ± 0.83	1.09 ± 0.74	<0.001
Endometrial thickness difference	2.92 ± 1.12	2.1 ± 0.98	<0.001

The mean PBAC score difference was 143.49 ± 19.94 in group A and it was 71.33 ± 28.97 in group B. The mean HB difference was 2.63 ± 0.83 in group A and it was 1.09 ± 0.74 in group B. The mean endometrial thickness difference was 2.92 ± 1.12 in group A and it was 2.1 ± 0.98 in group B. The mean difference was statistically significant (P value <0.001). (Table 5)

Discussion
Chhatrala et al. found 56.9% reduction in mean PBAC score in 6 months due to the effect of Ormeloxifene [9]. In study by Mandal et al, decrease in mean PBAC score was 57% with ormeloxifene and 49% with oral contraceptive pills after three months of treatment [10]. Khare et al also shows decrease in PBAC score of 18% with oral contraceptive pills and 47% with ormeloxifene [11].

In study by Sweta et al. [12], PBAC score was reduced by 79.9% with ormeloxifene (p value 0.001) and the rise in mean Hb level was 1.65g/dl (18.17%) In study by Dhananjay et al [13] in 35 patients with DUB showed that there was a statistically significant increase in Hb concentration (8.26 to 10.59 g/dl, p< 0.001) after 3 months of treatment with ormeloxifene.

Shahab et al. conducted a comparative study of ormeloxifene and norethisterone in 300 patients of DUB, 150 patients in each group. Ormeloxifene was given at a dose of 60mg twice weekly for 3 months followed by 60mg weekly for another 3 months whereas norethisterone was administered at a dose of 5mg twice a day continuously, 12 days in every cycle for 6 months. 123 (82%) women in ormeloxifene group and 45 (30%) in norethisterone group showed marked improvement of symptoms with significant reduction in PBAC score. Ormeloxifene showed better compliance and less number of women had to undergo hysterectomy14. Another study used a dose of 60mg ormeloxifene twice a week for 12 weeks followed by once a week for 24 weeks was conducted in 50 women with DUB. There was gain of more than 1% in hemoglobin and response rate was 87.5% by PBAC [15].

Singh et al. from Allahabad, Uttar Pradesh conducted a study of ormeloxifene in 172 patients of DUB. There was improvement in patients in term of absence of dysmenorrhea after treatment using ormeloxifene which blocks the action of progesterone [16].

Srilakshmi *et al*. reported that ormeloxifene alleviates patient's acceptability and compliance. They also concluded that oral administration of ormeloxifene showed a marked increase in relief of symptoms resulting in higher satisfaction [17].

Neha *et al*. studied 50 patients and found a rise in hemoglobin level (9.04 to 10.86), decrease in endometrial thickness (11.35 to 8.13) and PABC score ranging from 123 to 643 pretreatment and 0 to 75 at the end of 6 months of treatment with ormeloxifene [18].

A comparative study among COCs, ormeloxifene and norethisterone, Chauhan *et al*. [19] reported ormeloxifene to be better than COCs and norethisterone. In this study the authors used subjective PABC score and hemoglobin level for assessment of improvement in status of bleeding.

Agarwal and Singh *et al* have also found a significant decrease in ET and mean increase in Hb concentration by 6 months treatment with ormeloxifene [20]. Other drugs used for management of DUB are Danazole, Progesterone, GnRH analogs. Out of which GnRH is costly and associated with increased occurrence of Osteoporosis and vasomotor symptoms whereas Danazol is rarely used because of its adverse effects[21].

Conclusion
Both Ormeloxifene and OC pills are effective in reducing MBL, raising the Hb level and decrease in endometrial thickness. The results of this study indicate that Ormeloxifene provides effective pharmacological management more than OC pills and is suitable for DUB. It is well tolerated and a better alternative to hysterectomy in women who wish to maintain their reproductive functions.

Abbreviations
DUB: Dysfunctional Uterine Bleeding
PBAC: Pictoral Blood loss Assessment Chart
NSAIDs: Non-Steroidal Anti Inflammatory Drugs
SERM: Selective Estrogen Receptor Modulator
ER: Estrogen Receptor
COC's: Combined Oral Contraceptives
GnRH: Gonadotropin Releasing Hormones
MBL: Menstrual Blood Loss
ET: Endometrial Thickness

Acknowledgement

Declarations

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