REDUCED DOSE OF ORMELOXIFENE IN DYSFUNCTIONAL UTERINE BLEEDING-SAFETY AND EFFECTIVENESS

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ABSTRACT

AIM OF THE STUDY

To evaluate the effectiveness and safety of reduced dose of Ormeloxifene in the management of Dysfunctional Uterine Bleeding (DUB). Long term medical management for DUB, which is ideal and cost-effective is not yet available. Once it is available, it can revolutionise the management of DUB in developing countries. If Ormeloxifene is proved to be effective long-term at lower doses with minimal side effects, it can prevent the major number of blood transfusions and hysterectomies, which are common especially in the lower socioeconomic group of patients who cannot afford costly conservative measures.

MATERIAL AND METHODS

Out of 240 eligible patients with DUB, recruited from Gynaec OPD of CKM Hospital, Warangal, only 160 women consented to participate, out of which half of the patients were given the standard dose of Ormeloxifene that is 60mg twice a week for 3 months and once a week for 3 months (Group A). Half of the patients were given reduced dose of Ormeloxifene that is 30mg twice a week for all 6 months (Group B); 54 women from each group who completed the 6 months treatment and came regularly for followup were included in the present study. Both groups were matched for age and parity.

Pre-treatment PBAC (Pictorial Blood Loss Assessment Chart) scores were done for all cases and mean PBAC scores were calculated. Same was done at follow-up visits at 1 month, 3 months and 6 months. Side effects were looked for and TVS was done for Endometrial Thickness (ET)/Ovarian cysts. Haemoglobin estimation was done at the end of the study. Effectiveness was taken as reduction of mean PBAC score at the end of 6 months.

CONCLUSION

Mean PBAC scores at the end of 6 months, in each group showed a reduction of 86.64% of blood loss in group A (standard dose of Ormeloxifene) and 87.69% of blood loss in group B (reduced dose of Ormeloxifene). The reduction in both groups was similar. When the reduction in group A and group B was compared, the difference was not statistically significant [P = 0.33]. Hence, the lower dose schedule followed in group B can be recommended for management of DUB. This could make long term usage of Ormeloxifene more feasible when proved safe by larger randomised double blind studies.

KEYWORDS

DUB, Ormeloxifene, SERMs, PBAC Score.

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INTRODUCTION

Conservative methods for long term management of menorrhagia developed over the past many years like endometrial ablation by different methods, anti-fibrinolytic agents (Tranexamic acid), non-steroidal anti-inflammatory agents (Mefenamic acid) and Levonorgestrel releasing intrauterine device has given a lot of options to women suffering from DUB.¹ Progesterones, Danazol and GnRh analogs are also available, but unfortunately all these modalities are costly and most of the women in developing countries cannot afford them especially long term.²

In the past few years with the advent of Ormeloxifene, which can be afforded by the under privileged also, there is good hope for conservative management of menorrhagia without surgical intervention in developing countries like India. Ormeloxifene was first introduced in India in 1991 as a contraceptive-Saheli. It was actually launched by CDR Institute of Lucknow in 1991. There are no studies of Ormeloxifene in USA and UK and it is not approved in those countries yet. It was approved by FDA in India in 1992. It was later incorporated in family welfare program of India in 1995. It is also known as Centchroman.

Several studies in the past, have shown the efficacy of Ormeloxifene in the management of DUB. The advantages of Ormeloxifene are its efficacy, only minor side effects, patient compliance and cost effectiveness.^{3,4} Ormeloxifene does not have serious side effects like venous thromboembolism, which is one of the major side effects when DUB is treated with hormones.

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However, there are concerns about occurrence of ovarian cysts and endometrial hyperplasia with Ormeloxifene.⁵

The long term safety of Ormeloxifene used for more than 1 to 2 years is yet to be proved. Since side effects could be dose related, we have attempted lowering the standard dose recommended and studied the efficacy and side effects with a lowered dose schedule.

Incidence of women seeking help for menorrhagia is about 20 to 30% in 35 to 50 years of age group.⁶ Menorrhagia causes disability due to severe anemia and its consequences. Many times blood transfusions are needed and we all know its risks and complications. DUB also leads to anxiety and stress which can lead to both physical, emotional and socio-economical problems.⁷

Ormeloxifene was found to be more effective than progestrogens in the management of menorrhagia.^{8,9} Progestrogens are ineffective in the treatment of ovulatory DUB.¹⁰

Ormeloxifene is a good option in DUB, because it is a SERM (Selective Estrogen Receptor Modulator) which acts as an estrogen antagonist on uterus and breast, but acts as a mild agonist on vagina, bone, central nervous system and serum lipids.^{11,12} and its beneficial effects makes it even more preferable. There is relief from dysmenorrhea in most patients treated with Ormeloxifene. It also maintains cognitive function of the brain, which may be particularly useful in perimenopausal women. Its estrogenic effect on bone also may be helpful in this age group.

ORMELOXIFENE

STRUCTURE

Ormeloxifene is non-hormonal and non-steroidal and belongs to the Benzopyran group.¹³ It is a third generation SERM.

Systematic (IUPAC) name. 1-[2-[4-[(3S, 4R)-7-methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl] phenoxy] ethyl] pyrrolidine.

Pharmacokinetics

It exerts a contraceptive effect and normalise bleeding from uterus by regularising expression of estrogen receptors. It is well absorbed by gastrointestinal tract. Peak serum levels are achieved in 4 hrs. Its half-life is approximately 170 hrs. and

hence can be taken once or twice per week. It is metabolised by the liver. Its concentration in uterus is next only to liver.¹⁴

Contraindications are hepatic dysfunction, hypersensitivity, pregnancy and lactation.

MATERIAL AND METHODS

This is a prospective study taken up at a teaching hospital, CKM Government Maternity Hospital attached to Kakatiya Medical College, Warangal.

Recruitment of the cases for study was done from September 2012 to June 2014. Women with history of menorrhagia attending gynaecological OPD were evaluated and those diagnosed as DUB were considered for the study.

All cases were subjected to routine investigations after taking detailed history and ultrasound was done to exclude any pathology. TVS was done to assess Endometrial Thickness (ET) in all cases. Endometrial aspiration was done if ET was 8mm or more, between 8 to 10 days of the cycle, if cycles were regular. In some, D and C was done in an attempt to control an episode of menorrhagia and histopathology obtained to exclude atypia or complex hyperplasia.

Approval from the institutional ethical committee was taken for the study.

Inclusion Criteria

- Women of age 30 to 50 years with history of menorrhagia.
- With or without history of previous treatment for menorrhagia.

Exclusion Criteria

- Presence of pelvic pathology.
- Fibroids.
- Adenomyosis.
- Endometriosis.
- PID.
- Adnexal masses/ovarian cysts >5cms.
- Endometrial biopsy showing atypia or malignancy.
- Post-menopausal bleeding.
- Severe anemia.
- Immune deficiency.
- Liver dysfunction.
- Renal impairment.
- Blood dyscrasias.
- Cervical pathology with CIN 3, atypia or malignancy.
- Cardiac disease and CNS disorders.

Dosage Schedule

The patients selected for study were divided into two groups.

Group A-Patients in this group received the standard dose as used in the previous studies, i.e. 60mg Ormeloxifene twice a week for 3 months followed by 60mg Ormeloxifene once a week for 3 months.

Group B-Patients in this group received reduced dose as follows-Ormeloxifene 30mg was given twice a week for the total 6 months of the study period.

No hormones or haemostatic agent was used during the study period.

Age, parity and BMI was noted and compared for both groups. All participants were taught how to fill up the PBAC Chart. It was also ensured that all used similar sanitary pads to ensure judicious comparison. PBAC score (Table 1) of more

than 100 was taken as menorrhagia. Two pre-treatment baseline cycles were taken for comparing and assessing the effectiveness of the treatment and PBAC Scoring.¹⁵ was done in all cases. PBAC scores were calculated again at intervals of 1 month, 3 months and 6 months and the results compared for both groups.

ET (Endometrial thickness) was assessed by TVS for all the cases before starting Ormeloxifene and at the end of 6 months after starting treatment. (Table 2) When patients had regular cycles, ET was done between 8 to 10 days of the last cycle or else at the end of the study period, i.e. 6 months after starting treatment and compared to the pre-treatment values (Table 5).

Haemoglobin levels were done as part of complete blood picture for all cases before including in the study and cases of severe anaemia <7g/dL were withheld from the study. Haemoglobin levels were again repeated at the end of 6 months. All patients with less than 10gms haemoglobin were given 60mg elemental iron and 500mg calcium and dietary advice for protein intake. Side effects were noted by taking detailed history and ultrasound scan at followup visits. Number of cases according to PBAC Score were estimated at 1 month, 3 months and at the end of 6 months study (Table 2, 3 and Fig. 2). Number of cases with <100 PBAC score were compared at the end of 6 months study for both groups.

Mean and SD was calculated for PBAC scores of both groups pre-treatment and again at the end of 1 month, 3 months and 6 months study and results compared. The periodic mean PBAC in two groups were compared using paired 't-test.' The mean ET in both groups also was compared using 't-test.' The p values were calculated to know if there was statistically significant difference in the efficacy of the dose schedules for Group A and Group B. The difference between the two groups with p value <0.05 was defined as statistically significant.

RESULTS

Out of 430 women with menorrhagia evaluated, 240 were eligible for the study. Only 160 women consented to participate, out of which half of the patients were given the standard dose of Ormeloxifene that is 60mg twice a week for 3 months and 60mg once a week for 3 months (Group A). Half of the patients were given reduced dose of Ormeloxifene that is 30mg twice a week for all 6 months (Group B); 54 women from each group who completed the 6 months treatment and came regularly for followup were included in the study. The average age and parity of women recruited was comparable in both groups. Age was 39.2 (range 30 to 50 yrs.) and parity was 2.3 (Range 1 to 5).

Number of patients were compared depending on PBAC Scoring, (Table 2). At the end of third month 42 (75.92%) patients in group A had scores less than 100 compared to 41 (75.92%) patients in group B (Table 3). This shows further comparable reduction in amount of blood loss in both regimes.

At the end of six months, 46 pts. (85.18%) had scores less than 100 in group A compared to 47 (87%) pts. in group B. (Fig. 1, Table 4). There was no significant difference between the two groups regarding efficacy.

Mean PBAC score in group A before treatment is 322 (126-450) and the mean PBAC score in group B is 325 (124-482). The majority of patients (50%) in group A and 51% of patients in group B scored between 275 and 400 before

treatment. Mean PBAC score in group A and mean PBAC score in group B before and after treatment for 1 month, 3 months and 6 months are depicted in Fig. 2. There was significant difference between the pre-and post-treatment mean PBAC scores in both groups (Table 5).

The mean PBAC scores at the end of 6 months study in group A were 43.04, whereas in group B it was 40.07 with (p value =0.3) indicating that there is no statistically significant difference with regard to reduction of PBAC scores between group A and group B (Table 6). Endometrial thickness showed reduction in most patients in group B, but in group A, 27% cases showed endometrial thickness of more than 10mm after 6 months treatment (Fig. 3, Table 7).

While 6 cases in group A showed ovarian cysts of 5 to 6cms, only 1 case in group B had an ovarian cyst at the end of 6 months study period (Fig. 4). Amenorrhoea occurred in 21 cases (38.9%) of group A and 18 cases (33.3%) of group B, which was helpful in improving the haemoglobin levels. Patients were initially counselled regarding this beneficial side effect and it was welcome relief for most patients. Haemoglobin concentration (g/dL) improved significantly in both groups with a mean increase of 2.42 in group A and 2.36 in group B. Side effects observed in our study are shown in Table 8.

DISCUSSION

Surgery is not the answer for young patients who still have not finished reproduction. Unfortunately, now in the modern times, planning pregnancy is unduly delayed by working women due to change of priorities. Hence, ideal medical therapy for those women with DUB is the need of the hour in such situations.¹⁶ Contraceptive action of Ormeloxifene is another advantage in these women who are not planning pregnancy yet.^{17,18}

In perimenopausal women, again, medical therapy should be the principle line of treatment. Surgery should not be the first preference in this age group because of the morbidity and mortality associated.¹⁹ Many times medical management for a limited period or repeated courses of medical therapy could avoid surgery in many women as they attain menopause during or sometime after medical treatment.^{16,14}

The present comparative study shows that the mean PBAC scores at the end of 6 months study period reduced from 322.13 to 43.04 and from 325.04 to 40.07 in group A and group B respectively. The reduction of menorrhagia as reflected by the reduction of mean PBAC scores as compared to the pre-treatment PBAC scores is 86.64% and 87.69% in groups A and B respectively.

The difference in reduction of menorrhagia is not statistically significant (p= 0.33). The response in both groups shows almost same efficacy. Initially after one month, only 62-64% of people responded, by the end of 3 months nearly 75% of the patients and later 85-87% showed PABC scores of <100 in both groups. In group A at the end of 6 months, ET <5mm in 16 pts. in group A compared to 25 pts. in group B. The mean of ET in group A is 2.8, whereas it is 2.1 in group B. The difference in endometrial thickness in both the groups is statistically significant (P=0.03).

Side effects of group A are comparable with the pilot study done in 2009 study (5) Group B showed less side effects (Table 8). This indicates that reduced dosage schedule used for

group B patients has a definite advantage of minimal side effects while not compromising with the efficacy.

Amenorrhoea was noted in 21 (Gr A) and 18 (Gr B) patients at the end of 6 months is comparable to other studies done. (Biswas et al. 17.64% of pts. showed amenorrhoea, Kripalini et al. 46%), Biswas et al. noted that most of the pts. who attained amenorrhoea were in perimenopausal age group. No such observation was seen in our study.

The beneficial side effects due to its anti-estrogenic effect on the breast and mild agonistic effect on bone, vagina and serum lipids make Ormeloxifene more preferable for treatment of menorrhagia. Studies were and are being done regarding the anti-breast cancer action of Ormeloxifene.^{20,21} It also has beneficial effect in patients with fibroadenomas and mastalgia.

The results of the present study with regard to reduction of menorrhagia when compared to other studies (Table 9) show similar outcomes in most of the studies.

When compared to the other SERMS available, Ormeloxifene does not have the disadvantage of estrogenic action on endometrium like Tamoxifen and the anti-estrogenic effect on vagina of Raloxifene.

Recent evidence indicates that each SERM has a unique array of clinical actions on all tissues having estrogen receptors. Therefore, any particular SERM has to be evaluated individually and conclusions drawn through appropriate clinical trials.²²

Control of menorrhagia with Ormeloxifene is also showing good success in cases with fibroids and adenomyosis and further studies will prove its role in those conditions.

CONCLUSION AND RECOMMENDATIONS

This study shows that the reduced dose schedule of ormeloxifene can be routinely used for DUB with same effectiveness and negligible side effects. Our study involved only limited number of patients and only for 6 months. Further studies for much longer periods could assure in future regarding the safety of this drug when used long term or for its repeated usage when menorrhagia recurs.

It is our sincere hope that in future an ideal SERM may be ormeloxifene would become the first line of treatment for menorrhagia.

Effective medical therapy has the potential to reduce surgical procedures like hysterectomy and endometrial ablation.²³ Safe medical management of DUB could then be community based with referrals reduced to those with some underlying pathology.²⁴

Future studies to show the benefits and safety of combination of Ormeloxifene with other modalities, viz. progestins, antifibrinolytics or non-steroidal anti-inflammatory drugs for initial rapid control when patients present with severe menorrhagia and severe anaemia may make surgery a rare indication for DUB in future.

Pads	1 point	For each lightly stained
	5 points	For each moderately stained
	20 points	For each completely stained
Clots	1 point	For each small clot (less than a rupee coin)
	5 point	For each large clot (more than a rupee coin)
	5 point	For each episode of flooding

Table 1: PBAC Score

PBAC Score	Group A n (%)	Group B n (%)
100-200	9(16.36%)	11(20.37 %)
200-300	27(50 %)	24(44.44%)
>300	18(33.34%)	19(35.185%)
TOTAL	54	54

Table 2: PBAC Scores as per n (%) Pre-Treatment

PBAC Score	After 1 Month		After 3 Months	
	Gr A n (%)	Gr B n (%)	Gr A n (%)	Gr B n (%)
< 100	34 (62.96%)	35 (64.81%)	42 (75.92%)	41 (75.92%)
100 To 150	14 (25.92 %)	12 (22.23 %)	8 (14.82%)	7 (12.96%)
>150	6 (11.12%)	7 (12.96%)	4 (7.4%)	6 (11.12 %)
TOTAL	54	54	54	54

Table 3: PBAC Scores n (%) at follow-up during study period

PBAC Score	Group A n (%)	Group B n (%)
<100	46(85.18%)	47(87.03%)
100 TO 150	5(9.25%)	3(5.55 %)
>150	3(5.55 %)	4(7.41%)
TOTAL	54	54

Table 4: PBAC Scores n (%) at the end of 6 months

Figure 1

Figure. 2

Group	Mean PBAC Score--Pre treatment	Mean PBAC Score at end of 6 mths study	T value	P value
GROUP A	322.13	43.04	20.808	<0.001
GROUP B	325.04	40.07	20.580	<0.001

Table 5: Comparison of Pre & Post Treatment Values at 6 Months

GROUP	Mean PBAC Score	T value	P value
GROUP A	43.04	0.416	0.33
GROUP B	40.07		

Table 6: Comparison of mean PBAC score of Gr A with Gr B at the end of 6 Mths

ET(mm)	Gr A	Gr B	ET(mm)	Group A	Group B
0-5	8	6	0-5	16	25
6-10	27	28	6-10	23	24
>10	19	20	>10	15	5
TOTAL	54	54	TOTAL	54	54

Table 7: Endometrial thickness before and after treatment (6 Mths)

Figure. 3

GASTROINTESTINAL 6	3
WEIGHT GAIN 4	2
HEADACHE 7	3
OVARIAN CYSTS 6	1
AMENORRHOEA 20	18

Table 8: Side Effects : Group A

Figure 4: Ovarian cysts detected at the end of 6 months

STUDY	DURATION	DOSAGE	REDUCTION IN MEAN PBAC SCORE %
BISWAS SL, et al. (2004)	6mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 3mths	85.7%
J. SHRAVAGE et al. (2009)	6mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 3mths	85.7%
Phase III drug trial India (unpublished product monograph) by Torrent Pharma	6mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 3mths	87.8%
KRIPALINI A. et al. (2009)	4mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 1mth	97.7%
PRASAD S. et al. (2000)	6mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 3mths	80-87.7%
N. AGARWAL et al. (2013)	6mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 3mths	90.4%
Our study Group A	6mths	60mg twice wkly for 3 mths f/b 60mg once a wk for 3mths	86.64%
Our study Group B	6mths	30mg twice wkly for 6 mths	87.69%

Table 9: Comparison with other studies where standard dose of ormeloxifene was used for 6 months

BISWAS et al.	87.5%
SHRAVAGE et al.	No significant reduction
N. AGARWAL et al.	Decrease in mean ET 3.08
DHANUNJAY B et al.	Decrease in mean ET by 3.47
TORRENT PHARMA	85.8%
OUR STUDY	Decrease in mean ET by 2.1

Table 10 : ET Reduction as shown in other study groups

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