

A Study of Efficacy of Ormeloxifene in the Pharmacological Management of Dysfunctional Uterine Bleeding

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ABSTRACT

Objective: This study was carried out to evaluate the efficacy of Ormeloxifene in the pharmacological management of dysfunctional uterine bleeding.

Design and Setting: A prospective study was conducted on women with dysfunctional uterine bleeding, who attended to out – patient department of Obstetrics & Gynaecology in a tertiary care general hospital.

Material and Methods: Women with DUB were diagnosed by presence of excessive, prolonged, or frequent intervals of bleeding for eight or more days, unrelated to anatomical lesions or systemic diseases. They were enrolled randomly and after baseline assessment each patient was treated with Ormeloxifene 60 mg orally twice a week for first 12 weeks, followed by once a week for another 12 weeks. The efficacy of the study drug was analyzed by comparing the baseline and post treatment PABC score, haemoglobin level, endometrial thickness, presence of

clots in menstrual blood and dysmenorrhoea. The data obtained was analyzed using the paired t-test and Z-test.

Results: There was significant decrease in median PABC score from baseline to 25th week of treatment follow-up and the reduction was found to be statistically significant ($p < 0.001$). There was also significant decrease in the mean endometrial thickness ($p < 0.001$) after treatment with Ormeloxifene when compared to mean baseline value. The difference in mean haemoglobin level is 1.3 gm/dl between baseline and post treatment levels and was found to be statistically significant ($p < 0.001$). There was significant improvement, 84% of patients had relief from dysmenorrhoea ($p < 0.001$). No major adverse events were experienced by patients in this study.

Conclusion: The results in this study indicate that Ormeloxifene, a non-steroidal, non-hormonal agent, provides effective and favourable pharmacological management option with least side effects, suitable for the treatment of dysfunctional uterine bleeding.

Keywords: Dysfunctional uterine bleeding, SERM, Ormeloxifene

INTRODUCTION

Dysfunctional uterine bleeding (DUB) is abnormal genital tract bleeding based in the uterus and found in the absence of demonstrable structural or organic pathology [1]. Altered hypothalamic – pituitary-ovarian function and /or local changes in PG production can give rise to DUB. It is typically characterized by heavy, prolonged flow with or without breakthrough bleeding. DUB is a diagnosis that does not apply to menorrhagia only, but also includes excessively prolonged and frequent bleeding (Menometrorrhagia). It occurs more frequently in anovulatory than ovulatory cycles [2]. Dysfunctional uterine bleeding is a common debilitating problem among women in all age groups and accounts for 20% of gynaecology office visits [3]. In spite of current development of a minimal invasive surgical approaches, the traditional hysterectomy is still the only suitable definitive therapy for those who have no further wish to conceive. Cause of abnormal uterine bleeding should be ascertained quickly and appropriate therapy instituted. Dysfunctional uterine bleeding is most often the result of endocrinological dysfunction which responds well to conservative treatment.

Even though a number of treatment modalities are available, a reliable drug for management of dysfunctional uterine bleeding should meet the requirements like drug should be effective, convenient to take, cost of the drug must be low, with minimal side effects and the drug should have longest safety margin. Selective estrogen receptor modulator drugs (SERM) popularly known as Designer estrogens, Fantasy estrogens because they selectively bind with high affinity to estrogen receptors and mimic the effect of estrogen in some tissues but act as estrogen antagonists in others.

Ormeloxifene (also known as centchroman) is one of the selective estrogen receptor modulators [4], or SERMs, a class of medications

which acts on the estrogen receptor. It is a non-steroidal, non-hormonal oral contraceptive which is taken once in a week. In India, Ormeloxifene has been available as a birth control product since the early 1990s. It mediates its effects by high affinity interaction with ER, antagonizing the effect of estrogen on uterine and breast tissue and stimulating effect on vagina, bone, cardiovascular system and central nervous system [5]. Ormeloxifene not only preferred as oral contraceptive, but also useful for management of dysfunctional uterine bleeding and advanced breast cancer [6]. In the pharmacological management of DUB the standard dosage is 60 mg orally twice weekly for a period of 12 weeks followed by weekly once in the next 12 weeks. The safety profile of Ormeloxifene is excellent with very few side effects like nausea, headache, weight gain, delayed or prolonged menstrual period. To the best of our knowledge very few studies available on Ormeloxifene for the treatment of Dysfunctional uterine bleeding. We therefore proposed to verify the efficacy of Ormeloxifene in the management of DUB.

MATERIAL AND METHODS

This is a prospective study of 24 weeks duration on 50 women with dysfunctional uterine bleeding, who attended to out-patient department of Obstetrics & Gynaecology at King George Hospital, Visakhapatnam, Andhra Pradesh, India. After getting approval from the Institutional Ethics Committee, newly diagnosed dysfunctional uterine bleeding patients of >18 years were randomly included in this study. The patients with pelvic pathology like endometriosis, fibroids, pelvic inflammatory disease, known case or suspected or with a history genital tract malignancy, lactating mothers, those with heavy bleeding necessitating emergency treatment, and those who were on estrogen, progesterone, testosterone or danazol, prostaglandin

synthetase inhibitors, antifibrinolytic therapy were excluded. Patients with history of hypersensitivity or allergy to Ormeloxifene were also excluded. The patients meeting the inclusion criteria were explained in detail about the nature of the study, its purpose, regimen, procedure and follow-up. Informed consent was taken from all the patients included in the study. At the screening visit, patients were examined and detailed menstrual history was obtained to determine patient's eligibility for enrollment in the study. After initial screening, the demographic data, past medical history, findings of physical and clinical examination were recorded in the case report form. Routine haematological investigations like CBC, CT, BT, thyroid profile, ultrasound abdomen, endometrial histopathology and liver functions tests were done. Patients meeting the inclusion criteria were treated with Ormeloxifene tablet 60 mg, twice a week. The total duration of the study was of 24 weeks for each patient. All the patients were advised to take study medication regularly, every Sunday and Wednesday for the first 12 weeks and then once a week for another 12 weeks. Treatment schedule was continued irrespective of menstrual periods. The patients were advised to come for follow-up at 4th, 8th, 12th and 25th week of treatment initiation or earlier if needed. The main outcome measures- menstrual blood loss, endometrial thickness, Hemoglobin levels were assessed at baseline and at the 25th week of study. Pictorial blood loss assessment chart (PABC) [7] was used to measure the menstrual blood loss, a method that correlates well with the alkaline haematin test [8]. The women were asked to use certain sanitary products which have been shown to have similar absorbent capacities [9], and record the number of sanitary products used each day and the degree of soiling of each pad used. Number and size of clots passed were also noted. Scores were assigned to different degree of soiling of sanitary products and number and size of clots passed [Table /Fig-1]. A PABC score of greater than or equal to 100 indicated a menstrual blood loss greater than or equal to 80 ml and was considered diagnostic for menorrhagia [7]. We also recorded the adverse events of the drug during the study and by questionnaire recorded the subjective assessment of passage of clots and dysmenorrhoea. Dysmenorrhoea was categorized as absent, mild, moderate and severe. The endometrial thickness was measured initially and 25th week of the study at premenstrual phase by transabdominal ultrasound scan which was done by radiologist. The data obtained was analyzed using the paired t-test and the difference between the two proportions of the nominal data was analyzed by Z-test.

RESULTS

Out of 63 patients enrolled, 50 completed the study and 13 lost the follow-up. Age of the treated patients ranged between 18 to 51 years and maximum number of patients were in the age group between 21 to 30 years (42%). [Table/Fig-2] depicts the demographic data of the patients in the study. Bleeding was more common in multipara, this may be due to altered pituitary ovarian function following delivery. [Table/Fig-3] represents that there was significant decrease of median PABC score from baseline to 25th week of treatment follow-up and the reduction was found to be statistically significant ($p < 0.001$). Twenty four out of fifty patients (48%) recorded mean PABC score of less than 100 at the end of study period. There was a significant reduction of endometrial thickness at the end of 25th week. The mean difference was found to be statistically significant ($p < 0.001$). Majority of patients had anaemia when enlisted into the study as defined by WHO (haemoglobin < 12 gm/dl). There was a significant increase in post-treatment haemoglobin level when compared to baseline haemoglobin level. The mean increase of 1.3 gm / dl of haemoglobin level was statistically significant ($p < 0.001$). 84% of patients had significant relief from dysmenorrhoea ($p < 0.001$). Presence of clots in menstrual flow is a clear cut evidence of abnormality associated with DUB. 59% of patients had significant

Pads	Lightly soiled	1
	Moderately soiled	5
	Saturated	20
Clots	Small (Size of a rupee coin smaller)	1
	Large (Larger than a rupee coin)	5

[Table/Fig-1]: PABC Scoring

Number	50	Symptoms of Dysfunctional uterine bleeding	
Mean age (years)	30.2 ± 8.2	Menorrhagia	22 (44%)
Marital status		Polymenorrhoea	5 (10%)
Unmarried	10 (20%)	Polymenorrhagia	12 (24%)
Married	40 (80%)	Intermenstrual spotting	4 (8%)
Parity		Metropathia Haemorrhagica	3 (6%)
Multipara	35 (87.5%)	Peri menopausal bleeding	4 (8%)
Nullipara	5 (12.5%)		

[Table/Fig-2]: Demographic characteristics of study group

Parameters	At Baseline		At Post treatment		p value
	Min	Max	Min	Max	
Median Pabc Score	253		104.5		$p < 0.001$ ($t = 51.34$)
	120	526	0	380	
Mean endometrial thickness	11.674		9.3		$p < 0.001$ ($t = 19.6$)
	8	15.3	6.5	12	
Mean Hemoglobin level (gm/dl)	9.2		10.5		$p < 0.001$ ($t = 11.53$)
	7.9	10.8	9.7	12.9	
Dysmenorrhoea	36 / 50		6 / 50		$p < 0.001$ ($Z = 6.078$)
Presence of clots	22 / 50		9 / 50		$p < 0.002$ ($Z = 2.810$)

[Table/Fig-3]: Main outcome parameter measurements

Type of bleeding	Number of Patients before treatment	Number of patients after treatment	Percentage of improvement
Cyclical bleeding	24	1	95.8%
Acyclical bleeding	15	2	86.6%
Continuous	11	2	81.8%

[Table/Fig-4]: Analysis of results in relation to type of bleeding

relief from passage of clots ($p < 0.002$). [Table/Fig-4] indicates that out of fifty cases Cyclical bleeding was most common and was observed between 21 to 30 years of age group. Acyclical bleeding was commonly seen in peri-menopausal women and below 20 years of age. During the study period there were no major side effects, the observed effects were amenorrhoea (10%), giddiness (4%), abdominal pain (4%), headache (2%), which did not require termination of treatment.

DISCUSSION

Dysfunctional uterine bleeding occurs more commonly in the first five years after a women starts menstruating and as she approaches menopause, but it can occur at any time period. For women with DUB who wish to retain fertility, pharmacological approaches are the only currently available options. Among the other pharmacological agents, some are effective only for anovulatory DUB, some are useful only for ovulatory DUB, and still others may be effective for both. Pharmacological agents such as NSAIDs, oral contraceptive pills, progestins, danazol, GnRH agonists and antifibrinolytic drugs all reduce menstrual blood loss, however, the assets are limited to the duration of treatment. In our study we have analyzed the efficacy of Ormeloxifene in patients with dysfunctional uterine bleeding and our results suggested that there was a significant reduction of menstrual blood loss, these results are similar to other studies [10,11]. The results of the present study showed that there

was a significant rise of haemoglobin level which was also similar to other studies [10-13]. when endometrial thickness was compared between baseline and post treatment period, there was a significant reduction of endometrial thickness with this drug. These results are similar to other studies [10-14].

Dysmenorrhoea is a frequent complaint more reported by most of the patients. In the present study a total of 36 patients reported dysmenorrhoea during initial week and by the end of the study only 6 patients reported improvement which was similar to other studies [10,11,13,15]. Although our sample size was small, we got significant reduction in menstrual blood loss. The ultimate aim of pharmacological management of dysfunctional uterine bleeding is to restore the natural cycle of orderly endometrial growth and shedding. The choice of treatment must be opted in relation to several factors like presence of anovulatory or ovulatory cycles and the need for contraception. Patients preference (particularly desire to avoid hormonal therapy), contraindications to treatment also play a major role. In spite of treatment advances, DUB is still a significant cause of morbidity and mortality. Current therapies frequently fall short of providing full remission, due to unwanted effects. At the end, the treatment opted should be started only after the benefits of the treatment are weighed against the risks. In this scenario Ormeloxifene being a non-steroidal, non-hormonal agent it targets the disease with favourable profile.

CONCLUSION

Ormeloxifene was found effective in reducing menstrual blood loss in patients with DUB. It was found to be an excellent drug in controlling the systems of dysfunctional uterine bleeding without effecting normal endocrinal and physiological parameters. Pharmacological agents such as NSAIDs, oral contraceptive pills, progestins, danazol, GnRH agonists and antifibrinolytic drugs, they reduce menstrual flow, however, the benefits are limited due to the duration of therapy and as single agent is not suitable to all age groups. We conclude that Ormeloxifene is suitable for the treatment of DUB, in all age groups with effective therapeutic efficacy and with least side effects, study also shows that the compliance of the patient is good because of convenient dosage schedule and no need for medicine intake every day. Further studies with large sample size is needed to throw light regarding the efficacy and safety of the agent.

ACKNOWLEDGEMENT

The authors are deeply indebted to all patients in this study, Dr Ganni Bhaskara rao, Chairman, Dr. Y. V. Sharma, principal, GSL medical college & General hospital, Rajahmundry for their whole hearted support in completion of this study.

REFERENCES

- [1] Bravender T, Emans SJ (June 1999). "Menstrual disorders. Dysfunctional uterine bleeding." *Pediatr. Clin. North Am.* 46(3): 545-53.vii.PMID 10384806.
- [2] Chen BH, Guidice LC. Dysfunctional uterine bleeding. *West J Med.* 1998; Nov 169(5): 280-84.
- [3] Awwad JT, Toth TL, Schiff I. Abnormal uterine bleeding in the perimenopause. *Int J Fertil.* 1993;38:261.
- [4] Annu M, Tendon, Goel I, Mati M, Singh, Mastan, Singh et al. "The effect of Ormeloxifene, a selective estrogen receptor modulator, on the biomarkers of the endometrial receptivity and the pinopode development and its relationship with the fertility and the infertility in Indian subjects." *Fertility and Sterility.* 2009;91 (6): 2298-307.
- [5] Shelly W, Draper MW, Krishna V, Wong M, Jaffe RB. The selective estrogen receptor modulators: an update on the recent clinical findings. *Obstet Gynecol Surv.* 2008;63(3):163-81.
- [6] Lal, J. "Clinical pharmacokinetics and interaction of centchroman--a mini review." *Contraception.* 2010 ;81 (4): 275-80.
- [7] Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol.* 1990;97:734-39.
- [8] Hallberg L, Nilsson. Determination of menstrual blood loss. *Scand J clin lab invest.* 1964;16:244-48.
- [9] Grimes DA. Estimating vaginal blood loss. *J Repord Med.* 1979;22:190-92.
- [10] Biswas SC, Saha SK, Bag TS et al. Ormeloxifene a selective estrogen receptor modulator, for treatment of dysfunctional uterine menorrhagia. *J Obstet Gynaecol Ind.* 2004;54(1):56-59.
- [11] Kriplani A, kulshresha V, Agarwal N. "The efficacy and safety of Ormeloxifene in the management of Menorrhagia: a pilot study." *J Obstet Gynecol.* 2009; 35(4): 746-52.
- [12] Dhananjay BS, Nanda SK. Role of sevista in management of uterine bleeding. *Journal of clinical diagnostic and Research* 2013;7(1):132-34.
- [13] Parveen rajora P, Vivek rajora. Comparative study between the outcome of only dilatation & curettage and the outcome of ormeloxifene after dilatation and curettage in dysfunctional uterine bleeding. *Journal of evolution of medical and dental sciences/ volume2/issue6/February 11,2013.*
- [14] Jyotsna sharvage, D. Mekhala et al. Ormeloxifene versus Medroxyprogesterone acetate(MPA) in the treatment of dysfunctional uterine bleeding: A Double blind randomized controlled trial. *Journal of south asian federation Obstetrics and Gynaecology,* January-April 2011;3(1) 21-24.
- [15] Sudha Prasad et al. Centchroman- A novel drug for DuB. *J Obstet Gynecol Ind.* vol. 50, No. 2: April 2000.

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Date of Submission: **May 03, 2013**

Date of Peer Review: **Jul 29, 2013**

Date of Acceptance: **Sep 16, 2013**

Date of Publishing: **Nov 10, 2013**

FINANCIAL OR OTHER COMPETING INTERESTS: None.