Original Article

DOI: 10.7860/JCDR/2012/4794.2687

The Role of Sevista in the Management of Dysfunctional Uterine Bleeding

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ABSTRACT

Objective: The complaints of excessive menstrual bleeding (menorrhagia) have a substantial impact on the gynaecological services and in most of the cases, no organic pathology is identified. Nonsteroidal anti-inflammatory drugs and tranexamic acid offer a simple therapy which has to be taken during menses, with reductions of 25-35% and 50% respectively in the Menstrual Blood Loss (MBL). Danazol and the gonadatrophin-releasing hormone analogues are highly effective, but their side-effects make them suitable only for a short-term use. In the present study, the role of ormeloxifene was studied in patients of DUB.

Materials & Methods: The subjects were diagnosed cases of DUB. After ruling out the possible causes of the abnormal uterine bleeding, a diagnosis of DUB was made and the treatment with ormiloxifene was started. The number of cases were 35 cases. The treatment with ormeloxifene was evaluated by measuring the Hb g/dl and the endometrial thickness before and after 3 months of treatment with sevista. Ormeloxifene was given in the dosage of a 60 mg tablet twice a week for 3 months, followed by once a week for another 3 months.

Observation & Results: There was a statistically significant increase in the Hb g/dl ($p < 0.001$) and a statistically significant decrease in the endometrial thickness ($p< 0.001$) after the treatment with ormeloxifene.

Conclusion: Ormeloxifene can be used asa effective drug in the treatment of Dysfunctional uterine bleeding.

Key Words: Ormeloxifene, Dysfunctional uterine bleeding, Endometrial thickness

INTRODUCTION

Ormeloxifene (also known as centchroman) is one of the selective oestrogen receptor modulators, [1] or SERMs, a class of medications which acts on the oestrogen receptor. It is best known as a non-hormonal, non-steroidal oral contraceptive which is taken once per week. In India, ormeloxifene has been available as a birth control product since the early 1990s, and it is currently marketed here under the trade name, Saheli [1]. Ormeloxifene has also been licensed under the trade names, Novex-DS, Centron and Sevista. Ormeloxifene is primarily used as a contraceptive, but it may also be effective for dysfunctional uterine bleeding and advanced breast cancer. Ormeloxifene may be used as a weekly oral contraceptive [2]. The weekly schedule is an advantage for women who prefer an oral contraceptive, but they find it difficult or impractical to adhere to a daily schedule which is required by other oral contraceptives. For the first twelve weeks of use, it is advised to take the ormeloxifene pill twice per week [3]. From the thirteenth week on, it is taken once per week [3]. The consensus is that the backup protection in the first month is a cautious but a sensible choice. The standard dose is 30mg weekly, but the 60mg loading doses can reduce the pregnancy rates by 38% [4]. It has a failure rate of about 1-2% with an ideal use, which is slightly less effective than that which is found for the combined oral contraceptive pills [4]. Ormeloxifene has also been tested in experimental settings as a treatment for menorrhagia [5]. Its use in the treatment of mastalgia and fibroadenoma has also been described.There are concerns that ormeloxifene may cause urinary incontinence or a uterine prolapse.

METHOD OF ACTION

Ormeloxifene is a SERM, or a selective estrogen receptor modulator. In some parts of the body, its action is oestrogenic (e.g., in the bones). In other parts of the body, its action is anti-oestrogenic (e.g., in the uterus and the breasts [6,7]). It causes an asynchrony in the menstrual cycle between the ovulation and the development of the uterine lining, although its exact mode of action has not been well defined. In clinical trials, it caused the ovulation to occur later than it normally would, in some women [4], but did not affect the ovulation in amajority of the women, while causing the lining of the uterus to build more slowly. It speeds the transport of any fertilized egg through the fallopian tubes more quickly, than is normal [4]. Presumably, this combination of effects creates an such an environment that if fertilization occurs, an implantation will not be possible [4].

The hypothesis of the present study was that ormiloxifene was effective in the management of dysfunctional uterine bleeding. In the present study, the role of sevista (ormeloxifene) was studied in the patients of DUB by estimating haemoglobin and by measuring the endometrial thickness before and after the sevista treatment.

MATERIALS AND METHODS

The subjects were diagnosed cases of DUB. The number of cases were 35 cases. The main presenting complaints were bleeding PV, pain in the abdomen, a white discharge and irregular menstrual cycles. The mean age of the study group was 45 + 5 years. An institutional ethical clearance for the study was taken. An informed consent was obtained from the patients who were selected for the

study.The subjects were selected randomly. A history of the parity was obtained. All the patients were multiparous women . 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 the complete blood count, coagulation profile, thyroid profile, ultrasonogram of the abdomen and the pelvis and dilation and curettage. After ruling out the possible causes of the abnormal uterine bleeding, a diagnosis of DUB was made and the treatment with ormiloxifene was started. The treatment with sevista was evaluated by measuring the Hb g/dl and the endometrial thickness before and after 3 months of treatment with sevista. Sevista was given in the dosage of a 60 mg tablet twice a week for 3 months, followed by once a week for another 3 months.The endometrial thickness was measured in the premenstrual phase and it was measured by a transabdominal ultrasound scan which was done by a radiologist.

RESULTS

The details of Hb g/dl and endometrial thickness are given in [Table/Fig-1] and [Table/Fig-2]. The P values which were obtained by using the Student t test (Paired), were presented in Mean ± SD.

There was a statistically significant increase in the Hb g/dl ($p < 0.001$) and a statistically significant decrease in the endometrial thickness ($p < 0.001$) after the treatment with sevista.

Hb g/dl	Pre-treatment	Post-treatment	P value
Min-Max	6.50-9.80	9.60-11.50	Mean difference= 2.34 t=14.279 P<0.001**
Mean ± SD	8.26±0.89	10.59±0.48	
95%CI	7.94-8.57	10.42-10.76	

[Table/Fig-1]: Evaluation of treatment based on Hb g/dl

Endometrial thickness	Pre-treatment	Post-treatment	P value
Min-Max	4.20-14.40	2.00-9.00	Mean difference =3.47 t=7.768 P<0.001**
Mean ± SD	8.36±2.36	4.89±1.60	
95%CI	7.55-9.18	4.33-5.44	

[Table/Fig-2]: Evaluation of treatment based on Endometrial thickness

DISCUSSION

In the present study, our results suggested that there occurred a significant increase in the Hg g/dl and a significant decrease in the endometrial thickness. Our findings with respect to Hb g/dl, were in accordance with the findings which were obtained in the study which was done by Kripalini A et al.,. In the study which was done by Kripalini A et al., the menstrual blood loss was measured objectively by the Pictorial Blood Assessment Chart (PBAC) score and subjectively by using a Visual Analog Scale (VAS). Though in our study, we measured Hb g/dl and Kripalini A et al., measured PBAC, in both the studies, the blood loss was decreased after administering ormeloxifene.

Dysfunctional uterine bleeding is the diagnosis in a majority of the cases of menorrhagia. The symptom of menorrhagia accounts for a significant proportion of the referrals to gynaecologists. There is no hormonal defect in dysfunctional uterine bleeding; however, disturbances in the endometrial mediators have been noted. A majority of the cases are associated with ovulatory cycles when the cycle control is not an issue, and they can thus be treated with non-hormonal methods such as prostaglandin synthetase inhibitors and antifibrinolytics. Those patients with anovulatory cycles may benefit from an exogenous control of the pattern of bleeding by the use of hormonal preparations. When an effective contraception is also required, the use of either a combined oral contraceptive or the levonorgestrel releasing Intrauterine System (IUS) are the suitable choices. National guidelines exist for the management of menorrhagia. If appropriate attention is given to such guidelines, in addition to the individuals' symptoms and requirements, then the avoidance of inappropriate investigations, referrals and treatments may be achieved. The medical management of dysfunctional bleeding should ideally be based in the community. The referral to a hospital is reserved for those cases where the menorrhagia is thought to de due to an underlying pathology or when the initial treatment appears to fail [8].

Menorrhagia is an important healthcare problem. Its aetiology, investigations and medical and surgical management have been described. In approximately 50% of the cases of menorrhagia, no pathology is found at hysterectomy. Abnormal levels of prostaglandins or the fibrinolytic system in the endometrium have been implicated. The effective medical treatments which are suitable for long-term use include intrauterine progestogens, antifibrinolytic agents (tranexamic acid) and nonsteroidal anti-inflammatory agents (mefenamic acid). Over the past decade, there has been an increasing use of endometrial destructive techniques as an alternative to hysterectomy. Their further refinement and the advent of fibroid embolization has increased the options which are available for women [9].

A medical management is the first line of therapy for chronic menorrhagia. The agents that have been used to treat menorrhagia include iron, cyclooxygenase inhibitors, desmopressin, antifibrinolytics, gonadotropin-releasing hormone agonists, androgens, combined oral contraceptives, and progestins. Progestins can be administered systemically or locally and they may be given cyclically or continuously. The increased use of effective medical therapies has the potential to reduce the number of surgical procedures, such as endometrial ablation and hysterectomy [10].

The complaints of excessive menstrual bleeding (menorrhagia) have a substantial impact on the gynaecological services and in most of the cases, no organic pathology is identified. Up to 50% of the women who present with menorrhagia have blood losses within the normal range. A medical therapy is indicated for the patients who do not wish to undergo surgery, or for whom a surgery is unsuitable. Nonsteroidal anti-inflammatory drugs and tranexamic acid offer a simple therapy which can be taken during menses, with reductions of 25-35% and 50% respectively in the Menstrual Blood Loss (MBL). Danazol and the gonadatrophin-releasing hormone analogues are highly effective, but their side-effects make them suitable only for a short-term use. The combined oral contraceptive pill and the levonorgestrel intrauterine system give reductions of 50% and 80% in MBL, with an additional contraceptive cover. Cyclical progestogens are the most commonly prescribed therapy in the United Kingdom, but they are ineffective for the management of ovulatory menorrhagia unless they are taken at high doses (10-15mg daily) for 3 weeks out of [4,11].

Kripalani et al., studied the efficacy and the safety of ormeloxifene in the management of menorrhagia: it was a pilot study and it was found that Ormeloxifene was an effective and a safe therapeutic option for the medical management of menorrhagia [5].

The recent clinical data on the selective estrogen receptor modulators (SERMs) have provided the basis for the reassessment of the SERM concept. The molecular basis of the SERM activity involves binding of the ligand, SERM to the oestrogen receptor (ER), thus causing conformational changes which facilitate interactions with the coactivator or the corepressor proteins, and subsequently initiating or suppressing the transcription of the target genes. The SERM activity is intrinsic to each ER ligand, which accomplishes its unique profile by specific interactions in the target cell, leading to tissue selective actions. We have discussed the oestrogenic and anti-oestrogenic effects of the early SERMs such as clomiphene citrate, which were used for the treatment of ovulation induction, and the triphenylethylene, tamoxifen, which has an ER antagonist activity in the breast, and is used for the prevention and the treatment of ER-positive breast cancer. Since the development of tamoxifen, other triphenylethylene SERMs have been studied for breast cancer prevention, which include droloxifene, idoxifene, toremifene, and ospemifene. Other SERMs have entered the clinical development more recently, which include the benzothiophenes (raloxifene and arzoxifene), benzopyrans (ormeloxifene, levormeloxifene, and EM-800), lasofoxifene, pipendoxifene, bazedoxifene, HMR-3339, and fulvestrant, an anti-oestrogen which is approved for the breast cancer treatment. The SERMs have effects on the tissues which contain ER, such as the breast, bone, the uterine and the genitourinary tissues, and the brain, and on the markers of cardiovascular risk. The current evidence indicates that each SERM has a unique array of clinical activities. The differences in the patterns of action of the SERMs suggest that each clinical end point must be evaluated individually, and the conclusions about any particular SERM can only be established through the appropriate clinical trials [12].

Limitations of This Study: The number of the study group was less. A larger study group is needed. Hysteroscopy was not done. A long term follow up of the study group was not done.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Jul 02, 2012**
Date of Peer Review: **Jul 05, 2012**
Date of Acceptance: **Aug 27, 2012**
Date of Online Ahead of Print: **Sep 10, 2012**
Date of Publishing: **Jan 01, 2013**