

Tibolone versus Conjugated Oestrogen – What is the Short-Term Treatment Effect on Health-Related Quality of Life (HRQOL) in Surgical Menopausal Women?*

Sudhindra Mohan BHATTACHARYA

Vivekananda Institute of Medical Sciences, Kolkata, India

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Abstract

Objective: To study the effects of tibolone versus conjugated oestrogen as short-term treatment in improving HRQOL in surgical menopausal women utilizing Menopause Rating Scale II (MRS II).

Materials and Methods: Sixty four women were randomized to two groups. Women in Group A (32 women) received tibolone 2.5 mg daily and women in Group B (32 women) received conjugated oestrogen 0.625 mg daily. For baseline assessment of the severity of menopausal symptoms, each woman scored herself on the MRS II, and then again after three months and twelve months of follow up. All women returned for follow up after three months but only ten women in Group A and nine women in Group B returned for follow up after twelve months. As a very short-term therapy (first three months), women receiving tibolone were found to have slightly better overall quality of life compared to those having conjugated oestrogen (psychological symptoms were predominantly improved with tibolone).

Results: “Intent to treat” method of analysis showed that “probability” of relief and improvement of HRQOL after twelve months, were higher with tibolone than with conjugated oestrogen.

Discussion: In a very short-term treatment, tibolone improves psychological symptoms of menopause better than conjugated oestrogen and on further continuation of the therapy, overall chances of relief are more with tibolone.

Keywords: tibolone, conjugated oestrogen, health-related quality of life (HRQOL)

Özet

Konjüğe Östrojen ve Tibolon Tedavisinin Cerrahi Menopozlu Kadınlarda Sağlıklı Yaşam Kalitesine (HRQOL) Olan Etkisi Nedir?

Amaç: Kısa dönem konjüğe östrojen ve tibolon tedavisinin cerrahi menopozda olan kadınların HRQOL üzerine olan iyileştirici etkisini Menopoz Sınıflama Skalası II (MRS II) ölçeğine göre araştırmak.

Materyal ve Metot: Randomize olarak 2 grup için 64 kadın seçildi. Grup A’da günlük 2.5 mg tibolon kullanan 32 kadın, Grup B’de günlük 0.625 mg konjüğe östrojen kullanan 32 kadın yer aldı. Menopozal semptomların şiddetinin belirlenmesi için tedavi başında ve sonrasında 3 ve 12. aylarda MRS II ölçeği kullanıldı.

Sonuçlar: Bütün kadınlarda 3 ay sonra geri dönüş alındı, fakat 12 ay sonra Grup A’dan sadece 10 kadından, Grup B’den ise 9 kadından geri dönüş sağlandı. Kısa dönem tedavide (ilk 3 ay) tibolon verilen kadınlarla konjüğe östrojen verilen kadınlar kıyaslandığında, tibolon kullanan kadınların yaşamlarının genel kalitesinin az da olsa daha iyi olduğu saptandı (tibolonla birlikte psikolojik semptomlarda baskın olarak iyileşme görüldü). Bu analiz sonuçları göstermiştir ki, 12 ay sonraki HRQOL’de iyileştirme sayısı ve iyileştirme olasılığı tibolonda konjüğe östrojene göre fazladır.

Tartışma: Kısa dönem tedavide tibolon, konjüğe östrojene göre psikolojik semptomlarda daha iyi iyileşme göstermektedir. Uzun dönem kullanımlarda tibolonda genel olarak daha iyi sonuçlar alınmaktadır.

Anahtar sözcükler: tibolon, konjüğe östrojen, HRQOL

Corresponding Author: Dr. Sudhindra Mohan Bhattacharya

Flat 4, Mohona 5, New Raipur, Kolkata 700 084, India

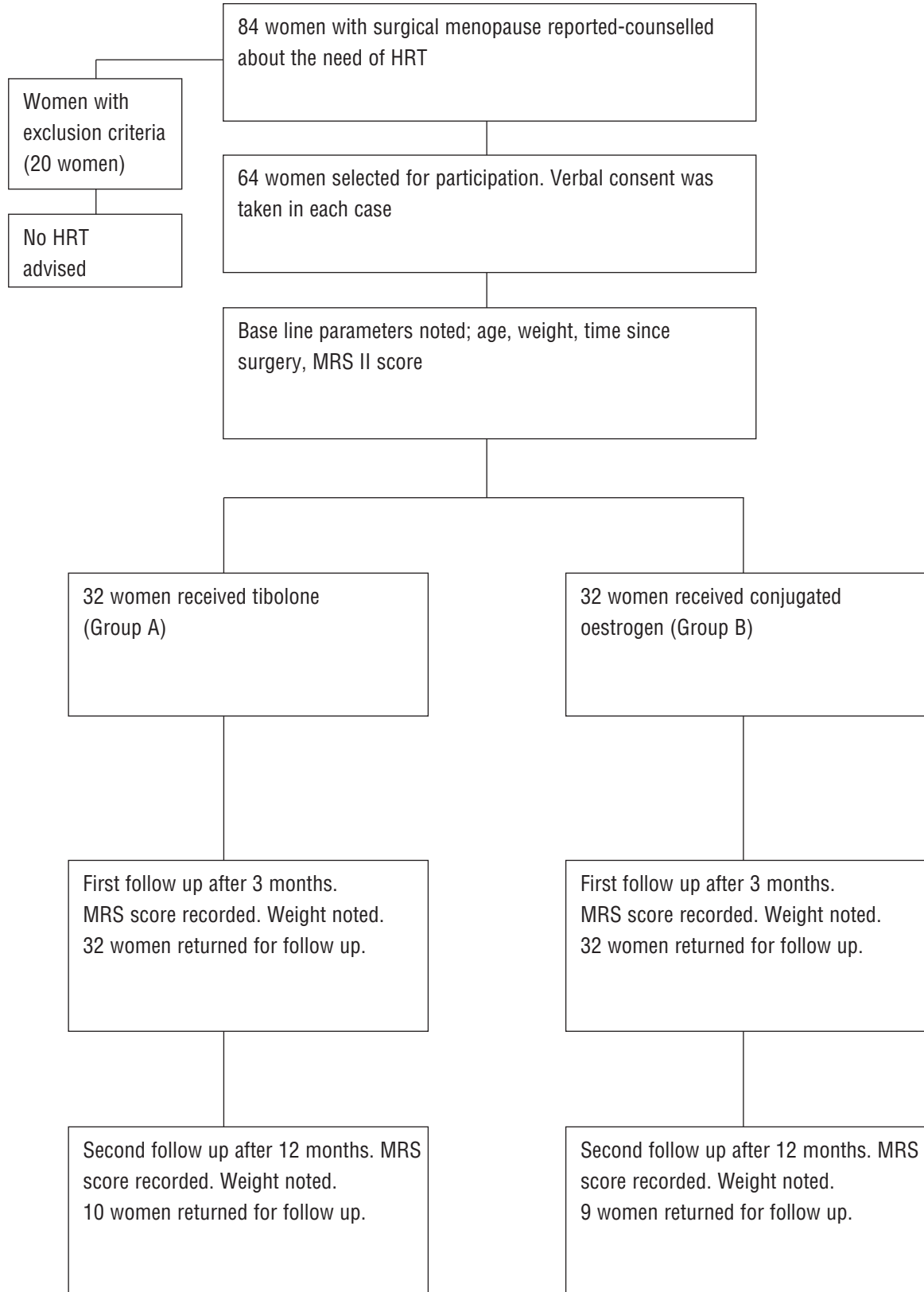
Phone : +91 33 243 034 00

GSM : +98 31 07 98 39

E-mail : sudhin@vsnl.net

*Part of the data was presented at the AOCOG 2007, Tokyo.

Flow Chart



Introduction

Surgical menopause in younger women can produce significant symptoms of oestrogen deficiency affecting the quality of life. Recently, patient evaluation by the health-related quality of life (HRQOL) has been given much importance, along with the traditional assessments of morbidity and mortality. HRQOL evaluates patients' satisfaction with a specific level of function and represents the functional effects of an illness and its treatment on a woman, as perceived by the woman herself (1). Nowadays, many clinicians are incorporating scales to assess HRQOL into their routine clinical practices and studies.

The Menopause Rating Scale II (MRS II) was developed in early 1990s in response to the lack of standardized scales to measure the severity of menopausal symptoms and their impact on HRQOL. A woman can easily interpret the scale herself. This MRS scale has shown to have high reliability, validity, excellent applicability and sufficiently good repeatability (2,3).

Use of hormone replacement therapy for menopausal symptoms and well being of menopausal women has been known to all gynaecologists and conjugated oestrogen has been used for this purpose for many years. Tibolone is a relatively new molecule used for the treatment of menopausal symptoms. It is a "selective tissue oestrogenic activity regulator". After oral administration, it is rapidly converted in the intestine and liver to two oestrogenic metabolites (3- α -OH-tibolone and 3- β -OH-tibolone), which are responsible for its oestrogenic effects on bone, vagina and climacteric symptoms, and a third metabolite, δ -4-tibolone, which has progestogenic and androgenic activities, that prevent endometrial stimulation (4).

Oestrogen as hormone replacement therapy is thought to be more advantageous than tibolone in treating women with surgical menopause, although it has not been confirmed (5). There are scanty studies on the effects of tibolone versus conjugated oestrogen on menopausal symptoms in women with surgical menopause utilizing MRS II.

The present study aims to compare the effectiveness of tibolone on HRQOL with that of conjugated oestrogen in women with surgical menopause, utilizing MRS II.

Materials and Methods

A prospective, randomised clinical observational study was done on women with surgical menopause (range 3-18 months following surgery) who attended the clinic of the author with distressing menopausal symptoms, from 1st of Jan 2005 to 31st of Dec 2005. All of these women

had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy performed by the author for various benign gynaecological conditions like, fibroid, dysfunctional uterine bleeding, endometriosis.

After counselling on the need of hormone replacement therapy for the relief of menopausal effects, 64 out of 84 women, who attended, were recruited in the study. Verbal consent was taken from each woman, and permission was taken from the Ethics Committee of SCDAS Memorial Medical and Research Center, Kolkata, India where the study was undertaken. It is a private non-teaching medical center where the author runs a gynecological clinic. In clinical practice in India, "verbal information and oral consent" is the routine practice. This same trend has been followed in the present study.

The 64 women who agreed for the study, were divided into two groups; Group A- 32 women who were advised to take Tibolone 2.5 mg daily (Livial®: Organon, Oss, The Netherlands), Group B- 32 women who were advised to take conjugated oestrogen 0.625 mg daily (Premarin®; Wyeth-Ayerst, Pennsylvania, USA). The first participant was asked to open one of two sealed envelopes, one containing name "Tibolone" and the other "Conjugated Oestrogen". Once she chose the envelope containing the name "Tibolone", every odd numbered woman received tibolone and even numbered woman received conjugated oestrogen.

Scale used to assess HRQOL

MRS II was used in each case. It lists 11 symptoms/complaints. Each symptom can be scored from 0 (no complaint) upto 4 points (most severe). The woman provides her personal perception of her symptoms by checking one of the five possible boxes of "severity" for each of the items.

The MRS II has three independent subscales; 1) Somato-vegetative symptoms, 2) Psychological symptoms, 3) Urogenital symptoms.

Each woman scored herself at the beginning of the study and then after three months and finally after twelve months of treatment. Body weight was recorded at each time of follow-up observation.

Exclusion criteria

1. Women who had already taken some form of oestrogenic preparations in the preceding three months (12 women)
2. Women with severe medical disorders like renal diseases, liver diseases, cardiac diseases, uncontrolled diabetes, uncontrolled hypertension, and history of venous thrombo-embolism (3 women)

3. Women with the histological reports of malignancy or premalignant conditions of the genital tract (1 woman)
4. Women already on psychiatric treatments (1 woman)
5. Women who did not agree for the study for fear of adverse effects of hormone replacement therapy as learned from magazines and the media etc. (3 women)

Outcome measures

Primary outcome measure was; improvement in HRQOL (Total MRS score and the three sub-scales).

Secondary outcome measure was; (1) compliance of the medications, (2) side-effects observed.

Statistical analyses

Nonparametric test was done for the data to assess the degree of improvement in total score and in the three subscales in the first three months when all the recruited women returned for follow up. Since there was a large number of dropouts in both of the groups, the “intent to treat” method was used for data up to twelve months to assess the “probability” of relief with treatments with the drugs in the two groups.

Results

All women returned for follow up after three months of treatment but only 10 women in Group A and 9 women in Group B returned for follow up after 12 months.

Reasons for the high rate of drop out were:

1. Cost. Both the drugs are costly in India (tibolone 9 cases; conjugated oestrogen 5 cases). After initial significant subjective improvement, many women declined to continue medications further for economic reasons. Women had to pay for the medicines.
2. Fear of long-term side effects, inspite of all assurances (tibolone 2 cases; conjugated oestrogen 5 cases).
3. Side effects;
 - Headache: Tibolone 2 cases, conjugated oestrogen 3 cases.
 - Mastalgia: Tibolone 1 case, conjugated oestrogen 4 cases.
 - Swelling of legs: Tibolone 3 cases, conjugated oestrogen 3 cases.
 - Chest discomfort: Tibolone 2 cases, conjugated oestrogen 3 cases
 - Hoarseness of voice: Tibolone 1 case only.
 - Sensation of weight gain: Tibolone 2 cases.

Table 1 shows the demographic characteristics of the two groups of patients. Both groups were comparable. Baseline MRS scores of the two groups were also comparable.

Table 2 “Intent to treat” group and Table 3 “All patients treated” group, indicate the changes in scores from baseline in the two groups.

Table 1. Demographic characteristics of the two groups of women

	Group A (Tibolone)	Group B (Conjugated oestrogen)
Number of women		
At the beginning	32	32
After 3 months	32	32
After 12 months	10	9
Age (years)		
Average (SD)	44.9 (4.3)	43.3 (3.1)
Range	38-52	38-50
Body weight (kg)		
Average (SD)	62.4 (8.4)	62.1 (8.6)
Range	48-76	39-77
Total MRS score at the beginning		
Average (SD)	25.3 (7.7)*	25.1 (4.3)*
SD: standard deviation. *p=0.8723 (not significant).		

Table 4 shows the nonparametric test analysis of the changes in the total score and that of the individual subscales of MRS in the first three months only. It shows the “probability” of relief in the three subscales and also the overall effect.

Results of the statistical analyses

- 1) The very short-term treatment (3 months); conjugated oestrogen improves somato-vegetative symptoms a little more than tibolone but for psychological symptoms, tibolone performs better. For urogenital symptoms, both drugs are equally effective. For overall effect, tibolone has a margin over conjugated oestrogen.
- 2) The “Intent to treat” method; The “Probability” of improvement was 97% at the end of first three months and 30% at the end of twelve months of treatment with tibolone compared to “probability” of improvements of 82% and 19%, respectively at the corresponding two points of assessments with conjugated oestrogen. This shows that tibolone performs better than conjugated oestrogen in short term treatment to improve HRQOL in surgical menopausal women.

Discussion

Surgical menopause causes an acute onset of menopausal symptoms and deterioration of HRQOL more than that following natural menopause.

Oestrogen as a hormone replacement therapy for the prevention of certain chronic ailments or relief of menopausal symptoms has been used for decades. The present consensus on the use of hormone therapy is to individualise the treatment according to the individual needs and preferences of each woman and to choose the

Table 2. Average values of the three subscales and the total score of MRS scale with the intent to treat* group

	Group A			Group B		
	a	b	c	a	b	c
Study points						
Somato-vegetative symptoms	9.3	4.6	3.8	10.0	5.1	4.9
Psychological symptoms	8.7	5.9	5.4	10.1	4.9	5.8
Urogenital symptoms	7.1	3.1	1.8	6.8	2.9	3.4
Total score	8.4	4.5	3.7	8.9	4.3	4.7

*Intent to treat group: women who received at least one dose of the study medication and had at least one on-treatment efficacy assessment.
a: score at the beginning.
b: score after three months.
c: score at the end of twelve months.

Table 3. Average values of the three subscales and the total scores at the three points of study with all patients treated* group

	Group A			Group B		
	a	b	c	a	b	c
Study points						
Somato-vegetative symptoms	8.7	4.6	3.8	10.1	6.2	4.9
Psychological symptoms	9.8	5.9	5.4	9.2	7.5	5.8
Urogenital symptoms	6.5	3.1	1.8	5.7	3.3	3.4
Total score	25.3	13.5	11.0	25.1	16.9	14.1

*All patients treated group: women having at least one dose of the study medication.
a: score at the beginning.
b: score after three months.
c: score after twelve months.

Table 4. Statistical significance of changes in the scores of the three subscales and the total score in the first three months of treatment

	Group A (n=32)		Group B (n=32)	
	Number reported improvement	Probability of relief	Number reported improvement	Probability of relief
Somato-vegetative symptoms	28	0.87	30	0.94
Psychological symptoms	26	0.81	19	0.60
Urogenital symptoms	24	0.75	24	0.75
Total score	30	0.94	26	0.81

Note: analysis of the data by testing of equality of proportions of relief reported to total, reveals a significant difference in favour of tibolone with $p < 0.02$.

optimal treatment option in terms of formulations, dose and route of administration. This treatment should aim to improve the HRQOL also.

In the present study, MRS II was used to assess the HRQOL. Gülseren et al. (6) had stressed the need for a menopause-specific instrument to measure the quality of life. Gülseren et al. (6), Mendoza et al. (11) reported their data after taking oral consents from the women, like the present study. This

is a single author and single clinic based study, which showed that the continuation rate is very poor at the end of twelve months, irrespective of the medication used.

In another study on tibolone, the author found that 85% cases dropped out at the end of twelve months of treatment (7). Continuation rate with HRT (hormone replacement therapy) at one year varies from country to country. In a developing country, it is still poor, as

found in the present study, inspite of all attempts to increase the awareness among the women. Samsioe (8) found that 54% of women on oral HRT continue for one year. Haines et al. (9) found that less than 8% of women were aware of HRT in southern China and Hong Kong.

The study is limited by the low number of women participating (32 in each group); short observation time and large number of dropouts. Absence of blindness is an important problem in studies on HRQOL and psychological symptoms. Heyerick et al. (10) reported a study on 67 menopausal women with a follow up of twelve weeks only. They found 27% dropout in the placebo group and 24% in the active group. Mendoza et al. (11) reported a study of 76 women. Somunkiran et al. (12) randomized 40 women and followed up initially for 6 months and then crossed over the treatment for further 6 months. Gülseren et al. (6) randomized 42 women and had a follow up of 6 months .

Role of androgen in postmenopausal women and women with surgical menopause is becoming more recognized, as the androgens have many important biological roles to play in women as well. Replacement of oestrogen only can cause a rise in SHBG (sex hormone binding globulin) levels; which further lowers the “free” testosterone levels. Thus, in spite of adequate oestrogenisation, there is a possibility of relative androgen deficiency. Tibolone on the other hand lowers SHBG and this adds to its intrinsic androgenicity (12,13). This mechanism can explain the greater improvements seen with tibolone than with conjugated oestrogen in the present study, particularly in the psychological symptoms, even in the first three months of treatment. This intrinsic androgenic effect of tibolone, in addition to its effect on β -endorphin levels in plasma and pituitary, should be helpful to alleviate the sexual problems and improve mood in menopausal women to assess which a specific questionnaire that addresses the sexual problems is needed. Somunkiran et al. (12) reported that tibolone treatment produced significantly greater improvements in psychological, somatic and sexual symptoms compared with oestrogen. Huber et al. (14) compared the effects of tibolone and conjugated oestrogen-medroxyprogesterone combination (CEE-MPA) on quality of life in 501 naturally menopausal women and found no difference in total “Green Climacteric Scale” score and psychological subscore between tibolone and CEE-MPA groups. Brunner et al. (15) reported that in surgically menopausal women, oral CEE (conjugated oestrogen) did not have a clinically meaningful effect on HRQOL.

In this study, side effects were noted more in Group B cases than in those in Group A. Though tibolone is more costly than conjugated oestrogen in India, continuation rate at twelve months showed no difference (10/32 in

Group A and 9/32 in Group B). This discards a greater preference for a less costly drug. The fear of undesired vaginal bleeding for discontinuation of HRT was nonexistent in this study, which recruited surgical menopausal women. Fear of long-term side effects with oestrogenic therapy is still prevalent among many women, inspite of all assurances. Since this is a clinic-based study and the women had to pay for the medicines, it is the usual trend to discontinue any costly drug once reasonable relief has been obtained.

In this study, the aim was to assess the effect of the two different treatments on HRQOL in surgical menopausal women. One can raise a question that hysterectomy itself may affect the HRQOL. But here the surgery was done in every case, for benign gynaecological conditions to enhance the quality of life. Studies have shown that in most women suffering from benign gynaecological conditions, quality of life is improved within a month after hysterectomy and the surgery does not produce any psychological disturbances in otherwise psychologically healthy women (16).

In this study with patients who had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy, 32 women received tibolone and 32 women received conjugated oestrogen. Compliance with the study protocol was very poor at the end of twelve months for different reasons. Statistical analyses showed that tibolone was as effective as or more than conjugated oestrogen in improving HRQOL in surgically menopausal women. Even in very short-term treatment, tibolone, because of its singular oestrogenic and androgenic actions, can help to improve the psychological symptoms. Therefore, tibolone can be a good alternative to HRT using oestrogen in women with surgical menopause, particularly if improvement in psychological symptoms is needed.

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Çetin SAATÇİ¹, Gökalp ÖNER², Sener TAŞDEMİR¹, Aslıhan KİRAZ¹, Yusuf ÖZKUL¹, Munis DÜNDAR¹, İptisam İpek MÜDERRİS²

Yazarların doğru sıralanması aşağıdaki gibidir:

Çetin SAATÇİ¹, Gökalp ÖNER², Sener TAŞDEMİR¹, Aslıhan KİRAZ¹, Yusuf ÖZKUL¹, Munis DÜNDAR¹, Okay A. ÇAĞLAYAN¹, İptisam İpek MÜDERRİS²

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