

Effect of Non-Hormonal Treatment on Uterine Leiomyoma

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Compliance with ethical standards

Conflict of Interest-Dr. Ramona Perhar, Dr. Osheen Bonal, Dr. Meena Dayal, Dr. Amrita Chaurasia, Dr. Rita Shukla declare that they have no conflict of interest.

Informed Consent- Informed consent was obtained from all individual participants included in the study.

Abstract: ***Aim:** To evaluate the efficacy of Non-Hormonal drugs on Uterine Leiomyoma* ***Method:** The study was conducted on sixty women of age 20-50 yrs with Leiomyoma. All cases were randomly divided into three groups, Group 1 received 25mg Mifepristone once daily, Group 2 received Ormeloxifene 60mg biweekly and group 3 received Tripterygiumwilfordii 30mg with Vitamin D 1000IU twice daily orally for 6 months. The efficacy of the drugs were analyzed by comparing the pre-treatment and post-treatment reduction in size of Leiomyoma, Pictorial blood assessment chart (PBAC), Visual Analogue Score (VAS), Haemoglobin level and Endometrial Thickness (ET).* ***Result:** A statistically significant reduction in PBAC score in group1 ($p < 0.0001$), group 2 ($P < 0.001$) and group3 ($p < 0.001$) and VAS (Mifepristone $p < 0.001$, Ormeloxifene $p < 0.001$ and Tripterygiumwilfordii with Vitamin D $p < 0.001$) was observed with equivalent efficacy. Hemoglobin level was significantly raised from 9.30 ± 1.34 to 11.57 ± 0.59 ($P < 0.003$), 9.40 ± 1.41 to 11.2 ± 0.66 ($p < 0.03$) and 9.51 ± 1.273 to 10.87 ± 3.49 ($P < 0.03$) in Group1, Group2 and Group3 respectively. Mean volume of Leiomyoma was reduced by 63.05% ($p = 0.001$) with Mifepristone, 25.79% ($p = 0.01$) with Ormeloxifene and 44.60% ($p = 0.001$) with Tripterygiumwilfordii with Vitamin D. A significant decrease in ET was 8.23 ± 0.68 to 5.39 ± 1.48 ($p = 0.001$) with Ormeloxifene whereas group1 ($p < 0.001$) and group 3 ($p < 0.05$) caused significant increase in ET.* ***Conclusion:** All the three drugs were found effective in treatment of Leiomyoma. However, Mifepristone was found to be more effective in reducing size of Leiomyoma and menstrual blood loss as compared to Tripterygiumwilfordii with vitamin D and Ormeloxifene with minimal side effects.*

Keywords: Leiomyoma Mifepristone Ormeloxifene Tripterygiumwilfordii

1. Introduction

Uterine Leiomyoma is monoclonal tumor of the smooth muscle cells of the uterus. An estimated incidence of Leiomyoma is 20%-40% in women during their reproductive years including symptomatic and asymptomatic conditions.^[1] The reported incidence ranges from 30% to 70% in premenopausal women and grows at an average rate of 1.2cm per 2.5 years.^[2] First degree relatives of women with Leiomyoma have a 2.5 times increased risk of developing Leiomyoma. The most common symptoms are heavy or prolonged menstrual bleeding, intermenstrual bleeding, pelvic pain caused due to pressure on pelvic organ, bladder pressure leading to frequent micturition, low back pain, dyspareunia and lump in abdomen. The treatment modalities for uterine Leiomyoma may include medical management which includes Hormonal and Non-Hormonal therapy that can antagonize the action of estrogen and progesterone.^[3]

Mifepristone (RU-486) has multiprong action on Leiomyoma. It binds strongly to endometrial progesterone receptor, minimally to estrogen receptor and upregulate androgen receptors and most importantly caused own regulation of progesterone receptors.^[4] Reduction in size of Leiomyoma with Mifepristone due to its direct effect in reduction of progesterone receptors in Leiomyomatous cells. It also inhibits or delay ovulation, which may produce amenorrhea. Direct suppressive effect on endometrial vasculature as well as on reducing stromal VEGF has also been suggested for reducing menstrual blood loss. Ormeloxifene is a third generation Selective Estrogen Receptors Modulator which has antagonistic action on uterine and breast tissue and agonistic effect on vagina, bone, cardiovascular and central nervous system. Antagonistic action on uterus help in reducing Leiomyoma size.^[5] Tripterygiumwilfordii is a traditional Chinese herb that is referred to as Lei Gong Teng but better known as Thunder

God Vine. It has therapeutic effects as anti-inflammation, anti-tumour, antifertility and immunoregulation. Triptolide, which is a metabolite, lowers estradiol and progesterone receptors in Leiomyoma, causing shrinkage of Leiomyoma. It led to inhibition of ovarian function, interruption of ovarian follicular development and produces amenorrhea.^[6]Triptolide inhibits Bcl-2expression, angiogenesis, and culture cell proliferation resulting in inhibition of Leiomyoma cell growth and promoting apoptosis. The inhibitory action of triptolide on aromatase, a terminal enzyme responsible for the formation of estrogens from androgens again reduces estrogen in uterine Leiomyoma.

2. Material and Method

The present study was done on Sixty women of age 20-50 yrs with symptomatic and asymptomatic Leiomyoma in Swaroop Rani Nehru and Kamla Nehru Memorial Hospital, M.L.N. Medical College, Allahabad over a period of 12 months

Inclusion Criteria

- Women with single or multiple Leiomyoma
- Women presenting with symptoms menorrhagia, dysmenorrhoea, abdominal lump, dull aching lower abdominal pain, dyspareunia

Exclusion criteria

- More than 20 week gravid uterine size,
- Leiomyomas >15 cm by ultrasound
- Suspected adenomyosis,
- Current genital infection,
- Endometrial hyperplasia with atypia, malignancy
- Hormonal therapy within 3 months,
- Hypersensitivity to the drug.

A detailed history was taken with special preferences to Age, Parity, Socioeconomic Status, Education, Personal habits and occupation. The menstrual history was specially focused on the cycle length, days and amount of bleeding during menses, presence of clots and associated dysmenorrhea or any hormonal contraceptive in past.

Objective assessment of menstrual blood loss was done by Pictorial Blood loss Assessment Chart PBAC is a simple and less time consuming procedure for objective assessment of menstrual blood loss. (Fig.1)




Pads		
1 point	For each lightly stained pad	
5 points	For each moderately stained pad	
20 points	For each completely saturated pad	

Figure 1: Pictorial Blood Assessment Chart

Patient were asked to note the degree of pain experienced by them in each menstrual cycle and to record it on the VAS scale provided to them. The correlation of the pain with the faces present in VAS scale was done. (Fig.2)

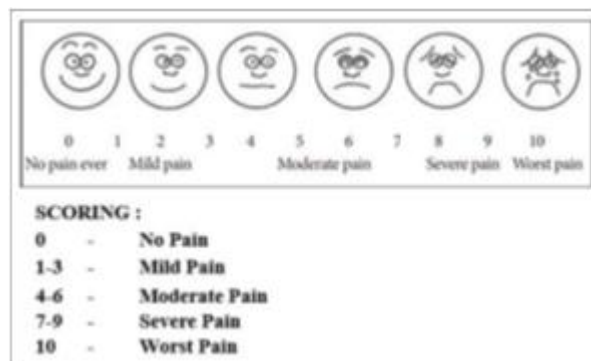


Figure 2: Visual Analogue Scale

Siemens sonoline G 50 equipped with Siemens EC9-4 transducer (6-9 MHz) was used High resolution ultrasonography with Doppler velocimetry for transabdominal ultrasonography. By USG the uterus was examined systematically and Leiomyomas were recorded if their minimum diameter was at least 0.5cm and could be visualized in all the three planes. For Transvaginalsonography preferably 6.5MHztransvaginalmicroconvex probe was used. Each individual Leiomyoma was measured with their 3 diameters (sagittal, longitudinal, transverse). Volume was calculated by the ellipsoid method with the formula $V= 0.5233 (D1 \times D2 \times D3)$ Endometrial thickness was measured in longitudinal axis, at the thickest point between the two basal layers on the anterior and posterior uterine walls.

The cases were divided into three groups. The first group included 20 cases who received Mifepristone 25 mg once daily for 3 and 6 months, second group included 20cases who were given Ormeloxifene 60 mg twice weekly for 3 months followed by 60 mg once weekly for another 3 months and 20 cases were given Tripterygiumwilfordii 30mg + vitamin D 1000 U twice daily for 3 months and 6 months in group 3.Follow up was done after 3 and 6 months of treatment and following observations were done - Heavy menstrual bleeding by PBAC Scoring, dysmenorrhoea by VAS Scoring, haemoglobin, size and number of Leiomyoma and side effects of drug and endometrial thickness.

3. Results

The most common age group affected by Leiomyoma was found to be in 4th decade between 36-40 years in all the three groups. Two third of cases 66.66% (40) were urban dwellers. More than half (58.3%) patients belonged to lower middle class. More than half (85%) women are literate. Most of the subject (91.66%) were married and were second para i.e. had low parity. (Table 1)

Table 1: Socio-demographic Data Characteristics

Variables	Number	Percentage
MEAN AGE (Years)	36.15±1.07	36.66%
RESIDENTIAL AREA		
URBAN	20	66.66%
RURAL	40	33.33%
MARITAL STATUS		
UNMARRIED	4	6.66%
MARRIED	56	93.33%
PARITY		
NULLIPAROUS	6	10%

MULTIPAROUS	47	78.33%
LITERATE	51	85%
MEAN BMI (kg/m ²)	24.14±3.04	53.33%

More than half (88.33%) cases presented with heavy menstrual bleeding at the beginning of treatment followed by dyspareunia (11.66%) and infertility (6.66%) while only 5% cases were asymptomatic. (Table 2)

Table 2: Clinical features among three groups at the beginning of treatment

Clinical Features	Group 1 (n=20)		Group B (n=20)		Group 3 (n=20)		Total	
	No.	%	No.	%	No.	%	No.	%
Asymptomatic	1	5%	1	5%	1	5%	3	5%
HMB	9	45%	11	55%	10	50%	30	50%
HMB with Dysmenorrhea	7	35%	8	40%	8	40%	23	38.33%
Dyspareunia	2	10%	3	15%	2	10%	7	11.66%
Pressure Symptoms	1	5%	-	-	1	5%	2	3.33%
Infertility	1	5%	1	5%	2	10%	4	6.66%

All the three drugs led to significant reduction in PBAC score with high efficacy at 3rd and 6th month of treatment. In groups 1 (Mifepristone) significant reduction in the mean PBAC score from 144.70 ± 52.25 to 41.8±36.929 (p<0.0001) was seen after 6 months of treatment. In Group 2 (Ormeloxifene) the mean baseline PBAC score at the time of enrollment was 163.10±42.4 and at the end of treatment of 6 months was significantly reduced to 45.50 ±24.67 (p<0.0001). In group 3 (Tripterygium Wilfordii with Vitamin D) significant decrease of mean PBAC score from 160.20 ± 35.23 to 61.20 ± 37.31 (P<0.0001) at 6 months of treatment was observed and the reduction was found to be statistically significant (Table 3).The mean VAS score was 2.70±1.49, 3.35±16 and 2.45 ± 2.03 in group1, group2 and group 3 which was significantly reduced to 0.95 ±1.91 (p<0.0001) 1.05 ± 0.99 (p<0.001) and 1.20 ± (1.005)

(p<0.01) in group1 (Mifepristone) group2 (Ormeloxifene) and group3 (Tripterygium Wilfordii with Vitamin D) respectively. Hemoglobin level was significantly raised from 9.30±1.34 to 11.57±0.59; (p<0.003), 9.40±1.41 to 11.2±0.66 (p<0.03) and 9.51±1.273 to 10.87±3.49 (p<0.03) by Mifepristone, Ormeloxifene and Tripterygium Wilfordii with Vitamin D respectively. All the three Non-Hormonal drugs found to be equally efficacious in raising hemoglobin levels.

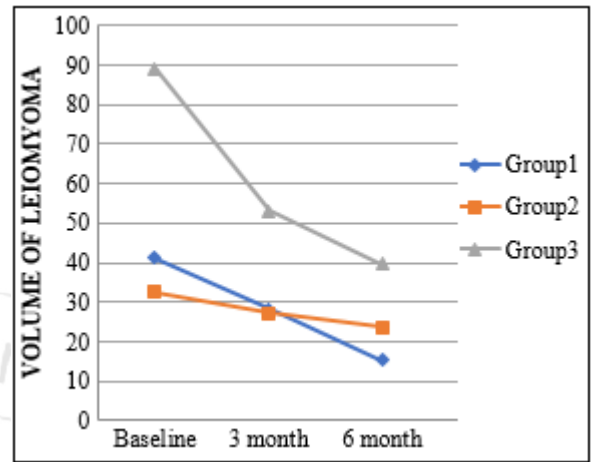


Figure 3: Volume of Leiomyoma At 0, 3 And 6 Months Of Treatment In Study Groups

Mifepristone caused a maximum reduction of 63.05% (p<0.0001) in size of Leiomyoma, Tripterygium Wilfordii caused a reduction of 44.60% (p<0.0001) whereas with Ormeloxifene was only 25.79% (Fig.3) Significant decrease in endometrial thickness was observed at 6th month of treatment 8.23±0.68mm to 5.39±1.48mm with Ormeloxifene whereas Mifepristone and Tripterygium Wilfordii with vitamin D caused increase in Endometrial thickness (p<0.001). (Table 3)

Table 3: Comparison of Clinical Features of Three Drugs at 0 and 6 Months of Treatment

Clinical Features	Group1 (n=20) Mifepristone	Group 2 (n=20) Ormeloxifene	Group 3 (n=20) Tripterygiumwilfordii with Vitamin D
PBAC Score Pretreatment mean	144.70±52.25	163.10±42.4	160.20±35.32
At 6 months	41.80±36.92	45.50±24.67	62.20±37.31
p value	p<0.0001	p<0.0001	p<0.0001
VAS score Pretreatment	2.70 ± 1.49	3.35 ± 1.630	2.45 ± 2.03
At 6 months	0.44 ± 1.68	0.20 ± 0.410	0.45 ± 510
p value	p<0.001	p<0.001	p<0.001
Hemoglobin (g/dl) Pretreatment	9.30 ± 1.34	9.40±1.41	9.51±1.273
At 6 months	11.57 ± 0.59	11.2 ± 0.66	10.87±3.49
p value	p< 0.003	p< 0.03	p<0.03
Size of Leiomyoma (cm ³) Pretreatment	41.316±34.35	32.52±21.10	89.046±98.635
At 6 months	15.27±9.74	23.59±9.31	39.705±21.70
p value	p<0.001	p<0.01	p<0.001
Endometrial thickness (mm) Pretreatment	6.11 ± 1.347	8.23 ± 0.68	5.94 ± 1.002
At 6 months	8.38 ± .78	5.39 ± 1.48	7.20 ± 0.57
p value	p<0.001	p<0.001	p<0.05

Maximum number of cases 41.66% cases developed amemorrhoea followed by infrequent menstruation seen in 36.66% cases as the common adverse effect. Non-hormonal drugs are associated with no major side effect and better to liability and compliance of patients. However amenorrhoea or infrequent menstruation are frequently

associated with Mifepristone and Ormeloxifene were less with Tripterygium Wilfordii with Vitamin D. (Table 4)

Table 4: Adverse Effects of Mifepristone, Ormeloxifene and Tripterygium Wilfordii with Vitamin D

Side Effects	Group 1 N=20		Group 2 N=20		Group 3 N=20		Total	
	No.	%	No.	%	No.	%	No.	%
No complain	1	5%	1	5%	2	10%	4	6.66%
Nausea and vomiting	1	5%	1	5%	2	10%	4	6.66%
Headache	-	-	2	10%	1	5%	3	5%
Abdominal pain	-	-	1	5%	1	5%	2	3.33%
Amenorrhea	17	85%	3	15%	5	25%	25	41.66%
Infrequent menstruation	1	5%	12	60%	9	45%	22	36.66%
Total	20	100%	20	100%	20	100%	60	99.98%

(p = 0.003)

4. Discussion

The development of medical management for Leiomyoma has established a firm place. If offered hysterectomy as a first treatment option some women choose to accommodate to symptoms and stop seeking treatment. This may lead to significantly worse scores on quality of life. Therefore, for women who are mildly or moderately symptomatic with Leiomyoma role on medical management have already been established. In our study the maximum age for Leiomyoma is in the perimenopausal age groups i.e. 36-40 years with low parity leads to more exposure to hyperestrogenic environment or use of hormonal contraceptive pills increasing risk for Leiomyoma. Heavy menstrual bleeding was reported by 88.33% women as the most common complain. All the three groups of non-hormonal drugs causes reduction in menstrual blood loss and symptomatic relief which improves the appetite of the women and compliance to oral iron products. The reduction in volume of Leiomyoma was maximum with Mifepristone as compared to the other two drugs.

Similar to present study, Seema Saharan et al (2016)^[7] found a statistically significant reductions in PBAC score from 111.52 to 2.36, mean VAS score 6.24±0.93 at the beginning of treatment to 1.28±0.74 and significant rise in Hemoglobin from 8.70±0.37g/dl to 11.08±0.48g/dl (p<0.001) with Mifepristone 25 mg for 6 months (p<0.0001). Similar study conducted by Vidushi Kulshrestha et al (2013)^[5] with a mean ET of 6.7 mm to more than 8mm after 6 months of treatment (p<0.05) with low dose Mifepristone. Similar results were obtained by Shikha Seth et al (2017)^[8]. She observed 53.62% reduction in volume of Leiomyoma with low dose Mifepristone in perimenopausal age group.

Also Dasgupta et al (2016)^[9] found statistically significant reduction with ormeloxifene from 184.41 t±84.92 to 8.3±55.46 after 6 months of treatment, significant reduction in VAS score from 7.41 ±0.8 to 1.60±0.8 (p=0.001) and significant increase in mean Hemoglobin from 9.19±0.789g% to 10.5±0.88 (p=0.001). She also observed a significant reduction in mean ET from 7.99 ± 1.16 to 7.12±1.15 (p<0.05) with Ormeloxifene. In contrast to present study Dasgupta et al (2016) found no change in size of with Ormeloxifene 60mg at biweekly dosage on 50 cases in West Bengal.

In accordance with the present study, Zhonghua et al (2000)^[10] conducted study on Tripterygium Wilfordii with vitamin D and found significant reduction of 51.6% in the size of Leiomyoma (p<0.001).

5. Conclusion

Non Hormonal drugs found to be useful and effective in reducing blood loss, shrinkage in size of Leiomyoma, improving hemoglobin levels and thus general condition of the women with single or multiple Leiomyoma. Mifepristone showed a speedy and better control of bleeding and alleviation of pain related symptoms with a few side effects. Mifepristone can be used for temporary relief of symptoms for short periods. This application is suitable in women with symptomatic Leiomyoma in peri- menopausal years who are not suitable for surgery.

Ormeloxifene in standard biweekly dosage is effective in preventing further growth of Leiomyoma, reducing menstrual blood loss when prescribed for a period of 6 months. Thus it may be used as an interim treatment to delay surgeries. This drug does not have significant side effects and is available at low cost.

Current evidence does not refute the use of *Tripterygiumwilfordii* with vitamin D due to insufficient studies but it showed a promising effect compared with Mifepristone as it shows a reversibly inhibitory effect on the ovary with minimal side effects. Although this study have shown that non hormonal treatment cause significant reduction in volume of Leiomyoma and alleviates the symptoms but further studies are needed for how long the benefits will sustain after discontinuation of treatment.

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