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Effectiveness of Mifipristone in the treatment of Uterine Leiomyoma

Dr. Y. Srilaxmi, MD, Associate Professor
Dr. G. Shailaja, MD, Professor and HOD
Department of Obstetrics & Gynaecology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India
Dr.Alla Satyanarayana Reddy, MD, Consultant in Reproductive Medicine, Hyderabad. India
Corresponding Author: Dr.Alla Satyanarayana Reddy, MD, Consultant in Reproductive Medicine, Hyderabad. India

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Abstract

Aim: To evaluate the efficacy of oral mifepristone in decreasing the severity of symptoms and in decreasing uterine and fibroid volume.

Methods: This was a prospective study conducted in the department of Obstetrics and Gynaecology, Prathima Institute of Medical Sciences, Karimnagar, Telangana. Fifty symptomatic patients with fibroids received 25 mg of mifepristone daily for 3 months . Baseline data regarding Hb value, pictorial blood loss assessment chart (PBAC), visual analogue scale(VAS), Uterine volume and Fibroid volume were compared with those recorded at the end of 1st month, 3rd month and 3 months after stoppage of mifepristone.

Results: Treatment with Mifepristone significantly reduced mean PBAC score by 95% after 1 month, 98% after 3 months and by 58% three months after completion of treatment compared to the pre-treatment value. Mean VAS score was reduced by 67% after 1 month, 72% after 3 months and by 47% three months after stoppage of drug to pre-treatment value. Mean uterine volume was reduced by 24% after 1 month, 44% after 3 months and by 35% in post treatment follow up patients compared to pre-treatment value. Mean baseline fibroid volume was reduced by 25% after 1 month, 54% after 3 months and by 40% in post treatment follow up patients. Though all these parameters slightly raised after stopping mifepristone, they are still significantly reduced compared to baseline values. Haemoglobin was raised by 2.12 gm/Dl from baseline at the end of 3rd month of therapy but slightly decreased compared to values of 3rd month treatment. Baseline endometrium was 7.4 mm which was increased to 8.24 mm after 3 months of treatment, it has come down to the baseline value which shows that endometrial thickness during treatment was transient. 88% of patients became amenorrhoeic after treatment but menstruation was resumed in 32.78% patients in post treatment follow up patients. There were minimal side effects during the course of study.

Conclusion: Low dose oral Mifepristone 25 mg for 3 months significantly reduced Menorrhagia, backache, dysmenorrhoea and other associated symptoms , decreased uterine and fibroid volume and improved Haemoglobin levels with minimal side effects.

Keywords: Mifepristone, Leiomyoma, Medical management, uterine volume, Fibroid volume

Introduction

Leiomyomas are the common uterine tumours seen in the women of reproductive age group. Its incidence is generally cited as 20-25%. Majority of fibroids are asymptomatic; however, when symptomatic --patients present with menstrual disturbances, infertility, lump abdomen or pressure effects. Management of fibroid can be surgical or medical. Among surgical options hysterectomy is viewed as the definitive management of symptomatic uterine fibroids. Myomectomy is an alternative for patients who desire child bearing, young patients and for those who prefer to retain uterus. There is a clear need for medical therapy that eliminates the need for surgery; as a pre operative step; and in those patients where surgery is contraindicated. Drugs available are anti-fibrinolytic tranexamic acid, Danazol, GnRH analogues, progestogens and various selective progesterone receptor modulators (SPRMS) like Mifepristone and Ulipristal acetate .

Danazol reduces uterine volume by 18-23% but is associated with marked androgenic side effects and liver dysfunction. GnRH reduces leiomyoma size to about 50% but is expensive and anti estrogenic leading to hot flushes, vaginal dryness and bone loss. Uterine artery embolization has been shown to decrease leiomyoma size by 35-69%, improves menorrhagia and reduces pain but there are potential risks of premature ovarian failure and uterine synechiae. Ulipristal acetate significantly reduces menorrhagia and size of fibroid but is expensive and there are reports of liver damage.

Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties, has been shown to decrease myoma size. It was proposed that growth enhancement of leiomyoma cells by progesterone was mediated via BCL-2 induction. Mifepristone reduces BCL-2, decreases EGF expression in uterine fibroid cells and increases TNF and thereby reducing fibroid size and uterine volume. Reduction in the size may be due to its direct effect on progesterone receptors. Increase in androgen receptors may also contribute to its effect on the reduction of the size of fibroid. As it inhibits ovulation it may produce amenorrhoea. It has a direct suppressive effect on endometrial vasculature and reduces stromal VEGF causing less menstrual loss.

25 mg dose of mifepristone has significantly greater reduction in size of myoma than 10 mg. This can be an optional treatment for younger patients who want to avoid surgery, in perimenopausal patients as well as an adjunct to surgery for size reduction.

Aims and objectives

The aim of the present study is to evaluate the effectiveness of low dose oral mifepristone (25 mg) on uterine fibroid and symptomatic improvement in decreasing severity of symptoms.

Materials and Methods

This prospective study was conducted in the Department of Obstetrics and Gynaecology, Prathima Institute of Medical Sciences, Karimnagar, Telangana during March 2016 to May 2017.

Fifty women in 20 to 50 years of age group with uterine fibroids of <7 cm on ultrasound. who wished to conserve their uterus were enrolled for study and written consent of patients was taken before including them in study. Permission from the institutional ethical committee was obtained. Women with fibroids >7 cm on ultrasound, use of hormonal medications within 3 months of starting the treatment, pregnancy, renal or hepatic dysfunctions, associated adenomyosis or endometriosis, endometrial report showing endometrial hyperplasia with atypia were excluded from study. A detailed history was taken regarding regularity of cycle, amount of blood flow, duration of flow. Menstrual blood loss was assessed by pictorial blood loss assessment chart (PBAC) scores, which is a semi-quantitative assessment that considers

number of pads soaked, degree of soakage, passage of clots and episodes of flooding. A score of 100 or more accounts to menorrhagia. The degree of dysmenorrhoea, abdominal pain, backache, and dyspareunia was estimated using Visual Analogue scale (VAS) score where patients were asked to describe their pain on a scale of 0 to 10 with no pain taken at zero and worst possible at 10.

A complete general and gynaecological examination was done. Haematological investigations included CBP, RBS, LFT, RFT, Thyroid profile. Ultrasound scan was done to look for uterine volume, fibroid volume, endometrial thickness and any other adnexal pathology. Viscosmi formula was used for the measurement of uterine volume that is 4/3 π × w/2× L/2 × T/2 (W is the uterine width on transverse section passing through the uterine fundus,T is distance between anterior and posterior walls L-uterine length on sagittal section from internal cervical os to fundus. measurement of fibroid volume was done by the formula 4/3π abc where a, b and c represent radii of the sphere in three dimensions. In multiple myomas volumes of largest 3 myomas more than 2.5 cm were added. Endometrium was biopsied in premenstrual phase at the start of therapy and repeated after 3 months of treatment. Each woman received T.Mifepristone 25 mg oral on day 2 or 3 of period and continued daily for 3 months. Total treatment was given for 3 months and data was recorded at every follow up visit i.e., after 1 month, 3 months and post treatment follow up was done at the end of another 3 months i.e., after 6 months.

Results:

Total 50 patients were recruited in the study.

Table 1: Baseline recordings of patients

Baseline recordings	Mean	Standard deviation
Age (years)	37.48	3.29
Parity	2.20	0.81
Durationof symptoms (months)	7.63	6.51
Haemoglobin(gm/dl)	9.30	0.31
Endometrial thickness(mm)	7.04	0.43
VAS score	6.0	1.95
PBAC score	122.84	37.07
Uterine volume(cm3)	217.58	71.15
Fibroid volume(cm3)	104.02	86.62

Majority of the patients were in the age group of 30-40 years with mean age 37.48 years, mean parity 2.2, mean Hb level 9.3 gm/dl. Mean duration of symptoms was 7.63 months, mean endometrial thickness was 7.04 mm. Mean baseline fibroid was 104.02 cm3 and uterine volume was 217.58 cm3.

Table 2: Comparison of symptoms at first visit and after three months of MIFEPRISTONE

Comparison of symptoms	At 1st visit		After 3rd month		Post treatment follow up after 3 months (stopping drug)	
	No of patients	Percentage	No of patients	percentage	No of patients	percentage
Menorrhagia	44	88%	0	0%	4	8%
Backache	32	64%	8	16%	12	24%
Dysmenorrhoea	18	36%	4	8%	8	16%
Lower abdominal pain	30	60%	2	4%	6	12%
Dyspareunia	2	4%	0	0%	1	2%

In total number of 50 patients at 1st visit Menorrhagia was recorded in 44(88%) patients, Backache in 32 (64%) patients, Dysmenorrhoea in 18 (36%) patients, Lower abdominal pain in 30 (60%) patients and Dyspareunia in 2 (4%) cases. After 3 months Menorrhagia was not seen, Backache in 8(16%) patients, Dysmenorrhoea in 4(8%) patients, Lower abdominal pain in 2(4%) patients and Dyspareunia was not noted. In post treatment follow up patients after 3 months of stopping the drug showed Menorrhagia in 4 (8%) cases, Backache in 12(24%) cases, Dysmenorrhoea in 8(16%) cases, Lower abdominal pain in 6(12%) cases. Dyspareunia in 1(2%) case.

Table 3: Pictorial blood loss assessment at first visit and follow up visits.

PBAC score	At 1st visit		After 1 month		After 3 months		Post treatment follow up after 3 months (stopping drug)	
	No of patients	(%)	No of patients	(%)	No of patients	(%)		
≤ 50	2	4%	46	92%	50	100%	36	72%
51-100	4	8%	4	8%	0	0%	14	28%
101-150	38	76%	0	0%	0	0%	0	0%
151-200	6	12%	0	0%	0	0%	0	0%
Mean± SD	122.84±37.07		6.2±5.90		2.03±0.72		52.03±12.05	

In our study mean PBAC score was 122.84±37.07 which was reduced to 6.2±5.90 i.e., 95% after 1 month 0f mifepristone and to 2.03±0.72 i.e., 98% after 3 months of treatment with mifepristone.in our series of 50 women, 46 became amenorrhoeic after three months, only four having monthly spotting. After six months, 38 women resumed spontaneous menstruation,but the bleeding was minimal. In post treatment follow up patients mean PBAC score was reduced to 52.03$\pm$12.05 *i.e.,* 58% compared to the pre-treatment value.

Table 4: Visual analogue scale at first visit and follow up visits.

VAS score	At 1st visit		After 1 month		After 3 months		Post treatment follow up after 3 months(stopping drug)	
	No of patients	(%)	No of patients	(%)	No of patients	(%)	No of patients	`(%)
No pain (0)	0	0%	2	4%	8	16%	4	8%
Mild pain (1-3)	2	4%	38	76%	42	84%	34	68%
Mod pain (4-6)	32	64%	10	20%	0	0%	12	24%
Severe pain(7-10)	16	32%	0	0%	0	0%	0	0%
Mean ± SD	6.0 ±1.95		2.6±1.41		1.60±1.04		3.2±1.08	

Mean baseline VAS scores at the time study was 6.0±1.95. It was significantly reduced to 2.6±1.41 (67%) at the end of 1 month and to 1.6±1.04 (72%). In post treatment follow up patients it was reduced to 3.2±1.08 (47%) from baseline.

Table 5: Endometrial changes before and after treatment

Endometrium	Before Treatment	After treatment
Normal endometrial proliferation	32	18
Atrophic endometrium disordered	0	0
Endometrium secretory hyperplasia	14	24
Simple hyperplasia	4	6
Cystic glandular hyperplasia	0	2
Complete hyperplasia without atypia	0	0

Endometrial biopsy before starting of Mifepristone showed normal endometrial proliferation in 36 cases, Endometrial secretory hyperplasia in 14 cases, and Simple hyperplasia in 4 cases. After 3 months of treatment endometrial biopsy was repeated which showed Normal endometrial proliferation in 18 cases, endometrial secretory hyperplasia in 24 cases, Simple hyperplasia in 6 cases, Cystic glandular hyperplasia in 2 cases?

Table 6: Uterine volume at first visit and follow up visits after mifepristone

Uterine volume (cm3)	1st visit		After 1 month		After 3 months		Post treatment follow up after 3months(stopping drug)	
	No of patients	(%)	No of patients	(%)	No of patients	(%)	No of patients	(%)
<100	2	4%	4	8%	6	12%	4	8%
101-150	4	8%	10	20%	14	28%	12	24%
151-200	8	16%	18	36%	16	32%	20	40%
201-250	14	28%	10	20%	8	16%	8	16%
251-300	12	24%	6	12%	4	8%	3	6%
301-350	6	12%	2	4%	2	4%	3	6%
351-400	4	8%	0	0%	0	0%	0	0%
Mean ± SD	217.58±71.15		164.48±61.38		122.03±78.04		142.06±52.02	

Mean base line uterine volume was 217.58 cm3, decreased to 164.48(24% less) after 1 month and further reduced to 122.03(44% less) tafter 3 months. In post treatment follow up patients mean uterine volume was reduced to 142.06(35% less) compared to pre-treatment value.

Table 7 : Fibroid volume at first visit and follow ups after Mifepristone

Fibroid volume (cm3)	At 1st visit		After 1 month		After 3 months		Post treatment follow up after 6 months	
	No of patients	(%)	No of patients	(%)	No of patients	(%)	No of patients	(%)
<50	22	44%	26	52%	36	72%	32	64%
51-100	16	32%	16	32%	12	24%	8	16%
101-150	6	12%	4	8%	2	4%	6	12%
151-200	2	4%	2	4%	0	0%	4	8%
201-250	2	4%	2	4%	0	0%	0	0%
>250	2	4%	0	0%	0	0%	0	0%
Mean±SD	104.02±86.62		78.04±42.08		48.03±39.05		62.08±38.04	

Mean baseline fibroid volume was 104.02 cm3 at 1 visit, reduced to 78.04 cm3 (25% less) after 1 month and further reduced to 48.03 (54% less) after 3 months which was significant. In post treatment follow up patients mean fibroid volume was 62.08±38.04 (40% less) compared to pre-treatment value.

The mean Haemoglobin at the time of treatment was 9.30±0.31 gm/dL. It was increased to 9.83±0.51 gm/dL at the end of 1st month and further increased to 11.42±0.34 gm/Dl at the end of 3rd month of treatment. In post treatment follow up patients mean Haemoglobin was 11.02±0.36 gm/DL.

Discussion

Symtomatic fibroids are accompanied with pain, bleeding, uterine abnormalities leading to deterioration in quality of life of patients affected by them. Surgical treatments are preferred as a last resort by the patients. Except hysterectomy none of the surgical treatments offer a recurrence free survival. Medical management is the treatment of choice who want to conserve the uterus and in perimenopausal women as fibroid being a hormone dependent tumor which stops to grow after menopause.

Current studies support that growth of fibroids in humans is progesterone dependent and therefore antiprogestins can be effective in treatment. One such drug is Mifepristone. Clinical trials using different doses of mifepristone 5-50 mg were conducted for varying periods 3 to 12 months in various studies and its usefulness was proved.

In this present study of 50 patients with symptomatic fibroids, oral Mifepristone 25 mg was administered daily for a period of 3 months and follow up was done after 1 month, 3 months of completion of drug and post treatment follow up was done after 3 months of stoppage of drug. Murphy et al reported comparative study of 5 mg, 25 mg and 50 mg and suggested 25 mg to be the most effective dose to cause significant decrease in leiomyoma. In this study majority of the patients were in the age group of 30-40 years with mean age 37.48 years. Majority of the women were parous, it has been shown that the incidence of uterine fibroids by age 35 is 60%, among African-American women increasing to more than 80% by age 50, whereas in Caucasian women reported this incidence to 46% by age 35 and almost 70% by age 50.

In our study all the women enrolled were symptomatic with majority of women having menorrhagia 88%, Backache 64%, Dysmenorrhoea 36%, Lower abdominal pain 60% followed by Dyspareunia 4%.

Comparison of amount of bleeding was recorded in all 4 visits using PBAC score. It was reduced by 95% after 1 month and by 98% after 3rd month of treatment with mifepristone which was significant. It was observed that mean PBAC score was reduced from 122.84 to 2.83 after 3 months. In post treatment follow up patients mean PBAC score was 52.03 (58% less) compared to pre-treatment value.

Kulshreshtha et al found mean PBAC score was reduced from 253 to 19.8(96.4%) in 25 mg daily group and from 289 to 104 in 10 mg group. In our study 46 cases (92%) became amenorrhoeic after treatment. Mechanism of reducing bleeding in myoma and myoma size is likely to be due to structural, functional and micro vascular effect of drug on the endometrium and uterine musculature in dose and duration. Shikha Seth et al reported amenorrhoea in 92.68% patients after treatment. Menstruation was resumed in a mean duration of 32.78 days. In the study of Shika seth et al, during post treatment follow up with 25 mg menstruation regained in a mean duration of

34.7±17.48 days. In our study 1 patient was amenorrhoeic at 3 months post treatment follow up.

The amount of pain felt by the patients were recorded on a pain analogue scale and observed 67% reduction of pain at 1st month, 72% reduction at 3rd month of study. In post treatment follow up patients there was increase in VAS score compared to score at the end of treatment but still reduced by 47% of pre-treatment value.

In the present study baseline mean endometrium was 7.4 mm which was increased to 8.24 mm after 3 months of treatment. Endometrial hyperplasia is a notable adverse effect of the drug. Long term use of high dose of ant progesterone may promote an unopposed oestrogen leading to endometrial hyperplasia.

Eisingar et al concluded 28% of patients developed simple endometrial hyperplasia. In post treatment follow up patients mean endometrium was 7.36 mm .It shows that increase in endometrial thickness is transient which reverts back to normal after stoppage of Mifepristone.

In this study uterine volume was reduced by 24% at the end of 1st month and 44% at the end of 3rd month.Eisinger SH et al reported reduction of uterine volume to 63.69% of baseline while B agaria et al reported 26.6% reduction with 10 mg over 3 months. In post treatment follow up patients uterine volume was reduced by 35% compared to pre-treatment value but there was an increase in uterine volume compared to treatment at 3 month. In Carbonell et al study uterine volume had doubled at 3 months post treatment follow up study compared to the end of treatment.

In this study reduction of fibroid volume was 25% at the end of 1st month, 54% at the end of 3rd month from baseline. Murphy et al observed 56% reduction in volume of fibroid with 25 mg mifepristone. Shikha seth et al reported 53.62% reduction in volume of fibroid. In post treatment follow up patients mean fibroid volume reduction was 40% compared to pre-treatment value but there was increase in volume compared to treatment at 3 month.

In our study Haemoglobin was raised by 2.12 gm/dL from the baseline of 9.3 gm/DL and haemoglobin was raised by 5.4% and 19% at the end of 1st and 3rd month of treatment respectively. Shika seth et al observed haemoglobin raise of 2.8 gm/dL in his study. Mean Haemoglobin was 11.02±0.3 in post treatment follow up patients which was slightly decreased in comparison with patients at the end of 3 months but it is raised by 16% to the pre-treatment value.

In present study there were no major side effects and so the compliance to drug treatment was good in all most all the studies including the present study.

Conclusion

Low dose of Mifepristone (25 mg) can be useful in treating symptomatic women with uterine leiomyoma in perimenopausal women and in patients not suitable for surgery due to medical reasons. Mifepristone is safe and effective drug in controlling bleeding, reducing discomfort in women with symptomatic leiomyoma and in decreasing fibroid and uterine volume.

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