

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20164498>

Original Research Article

Low dose mifepristone in the treatment of uterine leiomyoma

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Received: 30 November 2016

Revised: 05 December 2016

Accepted: 06 December 2016

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ABSTRACT

Background: To determine and evaluate the effectiveness of low dose of mifepristone in the management of symptomatic leiomyoma.

Methods: It is a randomized prospective observational before after treatment study of 50mg mifepristone once weekly for 24weeks (6 Months). The study was conducted at Navodaya Medical College Hospital and Research Centre, Raichur. The study period was Jan-June 2016; the total of 30 patients was enrolled in the study. Sample size was calculated to study changes in various parameters after 6months of treatment with mifepristone 50mg weekly. Basic investigations were performed, which includes Hb%, LFT, RFT, Complete Hemogram, USG examinations including Doppler study and menstrual blood loss was calculated through pictorial blood assessment chart.

Improvement of the patient was assessed at 1, 3 and 6 months.

Results: The majority of our study group patients belong to between 40-45 years and 66% of patients were para-2. The most important dominant symptom was menorrhagia, out of 30 patients, 27 had excessive blood loss during periods (90%). All 30 cases were subjected to endometrial biopsy before starting of treatment; there was a change in the endometrial pattern after treatment. The marked changes in the endometrium were simple endometrial hyperplasia and decrease in the normal endometrial pattern after treatment. In the present study after starting the treatment there was reduction in menstrual blood loss observed in 90% of patients and 75% of patients' attained amenorrhea at the end of treatment, improvement in haemoglobin parameter in the study group. The size of fibroids was also decreased.

Conclusions: Low dose mifepristone treatment for leiomyoma is more efficacious and useful to the patient. Drug helped in relieving the symptoms of the patient to a greater extent.

Keywords: Amenorrhea, Fibroid- Leiomyoma, Mifepristone, Medical management, Uterine volume

INTRODUCTION

The Uterine myoma is the common benign pelvic tumors, many a times it incapacitate women due to menorrhagia, dysmenorrhea, pelvic pain and other symptoms. The incidence cited as about 22-25% and majority of fibroid remains asymptomatic, when symptoms are present most important is menstrual disturbances, abdominal lump, pelvic pain, infertility and other pressure effects. Mifepristone is a selective progesterone receptor binding modulator with primary antagonist properties.

It binds to endometrial progesterone receptors minimally estrogen receptors and up regulates androgen receptors. In many of placebo control trials of Mifepristone has been shown to decrease myoma size and as well symptoms.¹⁻⁴ Reduction in the fibroid size with Mifepristone might be due to direct effect on in reducing the number of progesterone receptors. Increase in androgen receptors also contributes to the antiprogestronic effect. Mifepristone also delays or inhibits ovulation which may produce amenorrhea. Direct suppressive effect on endometrial vasculature as well as on reducing stromal vascular endothelial growth factor has also been suggested for reducing menstrual blood loss. Therefore this study designed to evaluate efficacy

and safety of mifepristone in medical management of uterine fibroid or leiomyoma.

The non-surgical treatment options for myoma are limited. Danazol reduces the volume of uterine fibroid but associated with marked androgenic side effects.

Gonadotrophic releasing hormones agonist reduces the size of myoma up to 50% but it is more expensive.

Uterine artery embolisation has been shown to decrease myoma by 35-60%, improves menorrhagia reduces the pelvic pain but there are potential risk of premature ovarian failure and uterine synechi.

METHODS

The randomized observational prospective before-after study was conducted on 30 patients having symptomatic leiomyoma. The study was undertaken at NMCH which is a tertiary care teaching hospital, Raichur.

This study was conducted between Jan 2016 to June 2016. Total 30 symptomatic patients were recruited for the study and written consent of patients was taken. A complete general; Gynaecological examination was done. Blood testing was done for hemoglobin, LFT, RFT were done. Ultrasound was done to confirm diagnosis and ascertain number site volume and measurement of endometrial thickness.

Fibroid volume was calculated by ellipsoid method and formula $V=0.5233 (D1, D2, D3)$ used. When D1, D2 and D3 are longitudinal, transverse and cross sectional diameters of the fibroid respectively. In multiple leiomyomas all volumes are added. Doppler ultrasound was done, the uterine artery resistive index (RI) and pulsatility index (PI) was noted. Endometrial aspiration was done before starting the treatment to know endometrial pattern. The clinical profile including menstrual cycle, symptoms and severity was noted.

The assessment of menstrual blood loss was done by pictorial blood loss assessment chart. It is a semi quantitative that takes into account of number of pads soaked, passage of clots. PBAC score more than 100 suggest more amount of bleeding that is menorrhagia. The tablets of mifepristone are available in the market in the strength of 200 mgs. Tablets are made into 4 portions and asked the patient to take $1/4^{th}$ every week. Patients are regularly followed at 1 month, 3 month and 6 month intervals, on every visit; clinical symptoms amount of bleeding and amenorrhea. Ultrasound was done to note down the number, size of fibroids and endometrial thickness.

RESULTS

The most important dominant symptom was menorrhagia, out of 30 patients, 27 had excessive blood loss during periods (90%).

Table 1: Age wise distribution.

Age (Yrs)	No. of cases	Percentages
30-34	5	17
35-39	10	33
>=40	15	50
Total	30	100

Table 2: Parity distribution.

Parity	No. of cases	Percentages
Nulliparous	2	6.67
Primiparous	8	26.67
Multiparous	20	66.67
Total	30	100.00

Table 3: Symptom wise distribution of cases and improvement.

Symptoms	Before treatment total cases	Reduction in symptom after treatment	
	No. of cases	No. of cases	%
Menorrhagia	30	27	90
Dysmenorrhoea	30	25	83
Pelvic pain	30	20	67
Urinary complaints	8	6	75
Dyspareunia	10	5	50

Table 4: Endometrial changes before-after treatment.

Endometrium	Before treatment	After treatment
Normal proliferation	18	12
Atrophic endometrium disordered	0	0
Endometrium secretory hyperplasia	8	2
Simple hyperplasia	4	12
Cystic glandular dysplasia	0	2
Complete hyperplasia without atypia	0	2

All 30 cases were subjected to endometrial biopsy before starting of treatment; there was a change in the endometrial pattern after treatment.

The endometrial changes specific to progesterone receptor modulator associated endometrial changes (PAEC) which includes cystic dilatation of glands with oestrogenic (mitotic) and progesterone secretory features, non-synchronous endometrium and abnormal

dilated thin vessels with no evidence of atypical endometrial hyperplasia

The marked changes in the endometrium were simple endometrial hyperplasia and decrease in the normal endometrial pattern after treatment.

In the present study after starting the treatment there was reduction in menstrual blood loss observed in 90% of patients and 75% of patients' attained amenorrhea at the

end of treatment. There is a Improvement in haemoglobin parameter in the study group.

The size of fibroids was also decreased (Table -6) and resistive index after treatment was raised due to loss of blood supply.

PBAC reduced significantly from 168 to 9.16 after starting the treatment and effect was noticed in the 1st cycle itself.

Table 5: Haemoglobin changes before-after treatment paired 't'-test.

Paired samples statistics				
	Mean	N	Std. deviation	Std. error mean
Haemoglobin(after)	10.9588	34	0.34034	0.05837
Haemoglobin(before)	8.4029	34	0.31955	0.05480

Paired samples test								
Paired differences								
Haemoglobin changes	Mean	Std. deviation	Std. error mean	95% Confidence interval of the difference		t	df	Sig. (2-tailed)
				Lower	Upper			
Haemoglobin (after) Haemoglobin (before)	2.55588	0.31545	0.05410	2.44582	2.66595	47.244	33	0.000<0.001**

P = 0.000<0.001 highly significant.

Table 6: Ultrasound changes before-after treatment.

Paired samples statistics				
	Mean	N	Std. deviation	Std. error mean
Ultrasound(before)	59.6147	30	45.47051	8.30174
Ultrasound(after)	26.8667	30	26.53005	4.84370

Paired samples test								
Paired differences								
Ultrasound examination	Mean	Std. deviation	Std. error mean	95% Confidence interval of the difference		t	df	Sig. (2-tailed)
				Lower	Upper			
Ultrasound (before) Ultrasound (after)	32.748	34.75311	6.34502	19.77097	45.72503	5.16	29	0.000<0.001**

P = 0.000<0.001 highly significant.

DISCUSSION

Mifepristone as a treatment for myoma was first reported by Murphy et al.¹ Further studies evaluated in doses varying from 2.5mgs to 50mgs given for 3 to 6 month and extended even up to 12 months.

The doses of mifepristone as high as 50mgs and as low as 5mgs were found effective in reducing myoma related symptoms.

The current study supports that growth of myoma is progesterone dependent also. Therefore antiprogesterone

drug like mifepristone which is a progesterone selective receptor modulator can be effective treatment.

The treatment with mifepristone improves the haemoglobin percentage from 8.4 to 10.95 which is statistically significant (Table 5).

Clinical trial using 2.5 to 50 mgs doses of drug were conducted for varying periods between 3 months to 12 months.

Eisinger SH et al reported fall of 48% in uterine volume while amenorrhoea in 61% after 6months of treatment.²

Kettle et al reported amenorrhoea 40 to 70% over 1 year treatment of 5 to 10mgs.³

In our study the dose of mifepristone was 50 mgs/weeks for 6 month the mean blood lose declined to 95% and 75% became amenorrhic, the mean blood lose PBAC score reduced to 9.16 from 168 in the 6 month study.

Kulshrestna et al found mean PBAC score reduced from 253 to 19.8 in 25 mgs daily group is 289 to 104 in 10mg groups.⁴

Mechanism of reduced bleeding in myoma and myoma size is likely to be due to structural functional and microvascular effect of drug on the endometrium and uterine musculature in dose and duration.⁵

In our study 50mgs of drugs reduced uterine volume and size very remarkable and ($P=0.000<0.001$ highly significant).

Morphy et al reported comparative study of 5mgs 25mgs and 50mgs suggested 25mgs to be the most effective dose to cause clinically significant decrease in leiomyoma.

Kapur A et al, studied efficacy of use of long term low dose mifepristone 50mgs/weekly for 6 month and concluded there was a much reduced in the size and volume of myoma.⁶

The antiprogesteron effect of mifepristone results in unopposed estrogen activity on the endometrium resulting in hyperplasia⁷.

With higher doses, activation of the hypothalamic pituitary axis may play a role. It has been showed that with higher doses drug induces rise in plasma ACTH is followed by an increase in not only plasma cortisol but also adrenal androgens and oestradiol. The peripheral aromatisation of adrenal androgen may lead to increased oestradiol level and contributes to the proliferation of endometrium.⁸

Out of 30 cases 12 cases had a simple endometrial hyperplasia 26.6%.

Endometrial hyperplasia is a notable adverse effect of the drug. Long term use of high dose of antiprogesterone may promote an unopposed oestrogen leading to endometrial hyperplasia.

Eisingar et al concluded 28% of patient developed simple endometrial hyperplasia.⁹

Mifepristone well tolerated drug with no serious adverse side effects (Spitz IM et al).¹⁰

In some cases biochemical hypothyroidism has been reported with long term administrations. Heikinheimo O et al in our series no cases have been reported.¹¹

Common side effects reported are mild hot flushes seen in 10-38%, Fatigue in 8-12%, and increase in liver Transaminase 4-7%. In our study mild hot flushes has been seen in 8%, fatigue 10% and there is no raise in the live transaminase level.

Written informed consent was taking from all recruited patients.

CONCLUSION

Low dose mifepristone treatment for leiomyoma is more efficacious and useful to the patient. Drug helped in reliving the symptoms of the patient to a greater extent. The primary medical line of treatment is limited due to recurrence after stopping the treatment. This treatment is more useful to especially for perimenopausal women whose myoma regress after attaining menopause it is also useful to a women who want to postpone the surgery in some extent and it is beneficial as pre-operative adjuvant.

They tolerated the drug very well and significant improvement in quality of life. Most important and useful effect of misopristone found to be the control of bleeding leading to improvement in Hb and general condition with side effects of endometrial hyperplasia.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Hangarga US, Rita D. Low dose mifepristone in the treatment of uterine leiomyoma. *Int J Reprod Contracept Obstet Gynecol* 2017;6:44-8.