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Original Research Article

A prospective clinical trial to evaluate the role of very low dose mifepristone 10 mg in medical management of uterine leiomyoma in tertiary care hospital from North West India

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ABSTRACT

Background: Uterine leiomyomas are the most common benign tumours of the uterus and also the most common benign solid tumor in female. It arises from the uterine smooth muscles (myometrium) but contain varying amount of fibrous connective tissue. Aim of study was to evaluate the efficacy of very low dose Mifepristone (10 mg) on leiomyoma volume and its related symptoms.

Methods: This was a prospective clinical study. 30 women met with the inclusion criteria and giving informed consent for the study.

Results: Mean myoma volume was 60.32 ± 51.89 at initial visit and 36.13 ± 48.54 at 3 months follow up visit with 40.1% reduction which was statistically significant difference ($p < 0.001$). Mean PBAC score in Group I was 155.53 ± 21.70 at initial visit and 0.97 ± 2.97 at 3 months follow up visit with 99.3% reduction which was statistically significant ($p < 0.001$).

Conclusions: Mifepristone 10 mg is efficacious in term of control of bleeding, alleviation of pain related symptoms with few side effects. So low dose mifepristone can be used as a suitable option for women with symptomatic fibroids in perimenopausal periods or patients not willing or fit for surgery.

Keywords: Leiomyoma, Mifepristone, Myoma volume, Perimenopausal

INTRODUCTION

Uterine leiomyomas are the most common benign tumours of the uterus and also the most common benign solid tumor in female. It arises from the uterine smooth muscles (myometrium) but contain varying amount of fibrous connective tissue.¹

The incidence cited as about 22-25% and majority of fibroid (50%) remains asymptomatic. When symptoms are present, the most important is menstrual disturbances. Other symptoms included abdominal lump, pelvic pain, infertility and other pressure effects. Fibroids are

responsible for 27% of gynecological admissions and are most frequent indication for hysterectomy.¹

If we give the choice to the patients, many women would opt for medical management that eliminates the need for surgery and which relatively cheap and has efficacy that is equivalent or superior to surgery. Mifepristone is a new promising agent gaining acceptance for treatment of fibroid. Mifepristone is a selective progesterone receptor binding modulator, with primary antagonistic properties. It binds to endometrial progesterone receptors minimally estrogen and upregulates androgens receptors. Appropriate dose for fibroid treatment is not clear. This

study was conducted to evaluate the efficacy of very low dose (10 mg) mifepristone in fibroid treatment.

METHODS

The present study titled was carried out in the department of obstetrics and gynecology, S. P. Medical College, Bikaner from 1st June 2018 to 30th September 2019. Thirty women meeting the inclusion criteria were recruited in the study after taking informed written consent.

Inclusion criteria

- Women between 20-50 years of age with single or multiple fibroids
- Women who are symptomatic (menorrhagia, dysmenorrhea, abdominal lump, dull aching lower abdominal pain, dyspareunia)
- Size of the largest fibroid be < 8 cm on ultrasound.

Exclusion criteria

- Ultrasound pelvis was done for all patients to exclude any other obvious causes like adenomyosis
- Endometriosis
- Adnexal mass for the above symptoms
- More than 20 weeks gravid size uterus, grade-0 submucosal fibroids
- Renal or hepatic dysfunction
- Suspected adenomyosis
- Current genital infection
- Endometrial hyperplasia with atypia and hormonal medication (progestogens/GnRH) within 3 months and women desiring pregnancy.

Demographic and baseline clinical profile including details of menstrual cycle, symptoms and their severity was noted. Menstrual blood loss was assessed by pictorial blood loss assessment chart (PBAC) scores, which is a semiquantitative assessment that takes into account the number of pads soaked, their degree of soakage, passage of clots and episodes of flooding. A score of 100 or more amounts to menorrhagia. Visual analog scale (VAS) score was noted for pain, dysmenorrhoea, dyspareunia, pelvic pain and pressure symptoms, where patients were asked to describe their pain on a scale of 0 to 10, before and after the treatment, with “no pain” taken at zero and “worst possible pain” at 10.

A complete general and gynecological examination was done. Blood testing was done for haemoglobin. Ultrasound was done to confirm the diagnosis of leiomyomas as well as to ascertain number, site, volume of myomas, to measure endometrial thickness and to rule out any other pelvic pathology.

Volume of each myoma was calculated and added in cases with multiple myomas. Fibroid volume was

calculated by the ellipsoid method and the formula $V = 0.5233 (D1 \times D2 \times D3)$ was used, where D1, D2 and D3 were the longitudinal, transverse and cross-sectional diameters of the fibroid, respectively. In multiple myomas, volumes of all myomas were added. Endometrial aspiration was performed to rule out any abnormal histopathology.

Sample size of 30 women was selected. Mifepristone was given as 10 mg/day, starting initially from day 2-3 of periods. Duration of treatment was 3 months.

Since mifepristone is available in India for indication of medical abortion as 200 mg tablet, capsules of 10 mg were prepared from 200 mg tablet in the Pharmacology department by crushing the tablets in powder form, and then filling the capsules according to the weight. Capsules of 10 mg could be prepared from 200 mg tablet without adding inert substance.

Patients were followed up after 3 months of therapy. On each visit clinical symptoms including bleeding and spotting, PBAC score, VAS score and any side effects were assessed. Amenorrhoea was defined as the absence of bleeding for two consecutive cycles. Ultrasound was done to determine the number of myoma and endometrial thickness.

At 3 months follow up; haemoglobin and ultrasound were repeated.

To collect required information from eligible patients a pre-structured pre-tested proforma was used.

Statistical analysis

For data analysis Microsoft excel and statistical software SPSS were used and data were analyzed with the help of frequencies, figures, proportions, measures of central tendency, appropriate statistical test.

RESULTS

The present study titled was carried out in the department of obstetrics and gynecology, S. P. Medical College, Bikaner 1st June 2018 to 30th September 2019. Majority of the patients belonged to the age group of 41-50 years. Mean age of the patients was 39.30±8.63 years. Mean parity was 3.20±1.52 (Table 1). Mean pain lower abdomen VAS score in group was 1.50±1.98 at initial visit and 0.50±0.94 at 3 months follow up visit with 66.7% reduction ($p < 0.001$). Mean dysmenorrhoea VAS score in Group I was 2.13±1.85 at initial visit and 0.20±0.55 at 3 months follow up visit with 90.6% reduction ($p < 0.001$). Mean backache VAS score in Group I was 2.53±2.01 at initial visit and 0.27±0.58 at 3 months follow up visit with 89.32% reduction (< 0.001) showing great effect on reduction in VAS score of pain related symptoms even with low dose of mifepristone (Table 2).

Table 1: Demographic profile.

Parameters		No. of cases	%
Age group (years)	20-30	6	20.0%
	31-40	8	26.7%
	41-50	16	53.3%
Residential area	Rural	21	70.0%
	Urban	9	30.0%
BMI (kg/m ²)	<18.5	0	-
	18.5-24.99	15	50.0%
	25.00-29.99	15	50.0%
	≥30	0	-
Parity	1	5	16.7%
	2	4	13.3%
	≥3	21	70.0%

Mean PBAC score in Group I was 155.53±21.70 at initial visit and 0.97±2.97 at 3 months follow-up visit with 99.3% reduction which was statistically significant ($p < 0.001$). Most of the patients become amenorrhea during the course of therapy. Mean myoma volume in Group I was 60.32±51.89 at initial visit and 36.13±48.54 at 3 months follow up visit with 40.1% reduction which was statistically significant difference ($p < 0.001$) showing greater effect on reduction in myoma volume even with low dose of mifepristone. Mean haemoglobin level in Group I was 8.77±0.78 at initial visit and 9.20±0.73 at 3 months follow-up visit with elevation in mean Hb level by 4.9% which was statistically significant ($p < 0.001$).

Side effects like leg cramps, hot flushes and nausea were observed in 2 cases, 2 cases and 1 case respectively.

Table 2: Association of VAS score (pain related symptoms) at initial visit and 3 months follow up visit.

Pain related symptoms (VAS)	Initial visit		3-month follow up visit		t-test	p value
	Mean	SD	Mean	SD		
Pain lower abdomen (VAS score)	1.50	1.98	0.50	0.94	3.942	< 0.001
Dysmenorrhoea (VAS score)	2.13	1.85	0.20	0.55	6.462	< 0.001
Backache (VAS score)	2.53	2.01	0.27	0.58	6.560	< 0.001

Table 3: Association of different parameters at initial visit and 3 months follow up visit.

Parameters	Initial visit		3-month follow up visit		t-test	p value
	Mean	SD	Mean	SD		
PBAC score	155.53	21.70	0.97	2.97	40.584	< 0.001
Hb (gm%)	8.77	0.78	9.20	0.73	6.574	< 0.001
Myoma volume (cm ³)	60.32	51.89	36.13	48.54	6.500	< 0.001

DISCUSSION

Myomas are benign tumour that develop in uterus. About 40% of women with fibroids have symptoms severe enough to warrant therapy. They are the most frequent indication for hysterectomy in perimenopausal women. As recently as 15-20 years ago, the choices for women with symptomatic fibroids were confined to abdominal hysterectomy and conventional abdominal myomectomy. So, there is clearly a need for medical therapy that eliminates the need for surgery, is relatively cheap and has efficacy that is equivalent or superior to surgery. At present, such medical therapy does not exist, but research is ongoing and promising avenues are opening up. Mifepristone is a new promising agent gaining acceptance for treatment of fibroid. However, till date, there is no fixed protocol of dose which should be used for treatment of fibroid. So, we conducted this prospective comparative study to compare the effect of very low dose of mifepristone 10 mg on the size of fibroid and myoma related symptoms.

In the present prospective comparative study, 30 cases meeting the inclusion criteria were selected. Mifepristone

was given as 10 mg/day daily for 3 months. The baseline data regarding the PBAC score, VAS score of pain related symptoms were compared at 3rd month of therapy with those recorded at the initial visit.

In this study, mean PBAC score at the time of enrolment was 155.53±21.70 and 153.83±46.47 in Group I and II respectively. The mean PBAC score was reduced by 99.3%. Reduction in PBAC score was significant at the end of treatment ($p < 0.001$) and the effect started at the very first cycle.

In the study conducted by Kulshrestha et al, PBAC score was reduced by 92.4% while 95.7% patients developed amenorrhea in 10 mg mifepristone group.² Saharan et al, observed 98% decrease in PBAC score with 10 mg/day dose of mifepristone at end of 3 months of therapy.³ Esteve et al, observed that amenorrhea developed in 93.6% patients at the end of therapy.⁴ Engman et al, and Singha et al, observed that 100% patients became amenorrhoeic at the end of the therapy.^{5,6}

The patients were followed for 3 months for the amount of pain lower abdomen, dysmenorrhoea and back pain on a

visual analogue scheme scale. There was 66.7% reduction in pain in lower abdomen VAS score at end of 3rd month of therapy.

A total 90.6% reduction in dysmenorrhea VAS score was observed at end of the 3 months therapy. 89.32% reduction in back pain VAS score was observed. The reduction in pain lower abdomen VAS score, dysmenorrhea VAS score, back pain VAS score was statistically significant.

Kulshrestha et al and Seth et al reported statistically significant improvement in pain in lower abdomen, dysmenorrhea and back pain in their study ($p < 0.001$).^{2,7} Saharan et al, and Esteve et al, (in 5 mg group) reported 79% and 85.7% reduction in VAS score at end of 3rd month respectively which is comparable to this study.^{3,8}

Treatment was well tolerated by all patients as evidenced by adherence of the patient to treatment. So, mifepristone in low dose can be considered as a good option for patient with symptomatic fibroid in perimenopausal group or in patients not willing for surgery.

CONCLUSION

Very low dose of mifepristone (10 mg) showed a significant reduction in myoma volume, showed a speedy and better control of bleeding and alleviation of pain related symptoms that improved the general condition of women, provided them a sense of well-being with a few side effects. Hence very low dose of mifepristone (10 mg) is also a suitable option in women with symptomatic fibroids in perimenopausal years or in patients not suitable for surgery.

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

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