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Original Research Article

A study on role of low dose mifepristone in the management of fibroid in reproductive age group women

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ABSTRACT

Background: Uterine fibroids are the most common benign uterine tumors occurring in 20-50% of women with maximum incidence between 35-45 years of age. Majority of fibroids are asymptomatic. When symptomatic, they present with abnormal menstrual bleeding, dysmenorrhea, chronic pelvic pain, abdominal heaviness, pressure symptoms etc. It is the commonest indication of hysterectomy worldwide. Mifepristone, an antiprogesterone is being widely used as one of the medical managements in potential symptomatic patients (mostly 10-20 mg daily doses).
Methods: An institute based prospective study including 100 reproductive aged women with symptomatic single uterine fibroid, was conducted over one-and-a-half-year period. They were administered 10 or 25 mg mifepristone daily for 3 months depending on fibroid size. Clinical parameters were assessed at initiation and at the end of their treatment.
Results: Our results showed that mifepristone (both 10 and 25 mg) led to symptomatic relief, with 96% reduction in menstrual blood loss and reversible amenorrhoea in 87% of the patients. Intramural fibroids responded more than submucosal fibroids in terms of relief of menorrhagia and improvement of haemoglobin (Hb) levels, with similar reduction in fibroid volumes of both intramural and submucosal locations.
Conclusions: Low dose mifepristone is an effective and safe drug for the medical management of uterine myoma. Due to the benign nature of fibroids, conservative management should be considered wherever feasible. Several clinical trials using 5-50 mg of mifepristone have been conducted over variable durations between 3-12 months but the exact dosage and treatment duration are yet to be decided.

Keywords: Mifepristone, Uterine fibroids, Myomas, Leiomyoma, Intramural fibroids, Submucosal fibroids

INTRODUCTION

Uterine fibroids, also called fibroid tumors, fibromyomas, myoma, leiomyofibroma, and leiomyoma, are the most common benign uterine tumors occurring in 20-50% of women with maximum incidence between 35-45 years of age.[1] The exact etiology is debatable, but the risk factors include younger age at menarche, obesity, nulliparity and African race.[2]

Majority of fibroids (upto 60%) are asymptomatic. The size, number and location of leiomyomas determine their wide clinical presentations like abnormal menstrual bleeding, dysmenorrhea, chronic pelvic pain, sensation of abdominal heaviness, aesthetically unacceptable abdominal enlargement, pressure symptoms such as increased urinary frequency and bowel disturbances.[2] The diagnosis is mostly done by ultrasonography (USG), Doppler studies and even magnetic resonance imaging (MRI) when in doubt. The complications may include severe anemia requiring blood transfusions, urinary retention, obstructive uropathy leading to hydronephrosis, hyaline or red degeneration and rarely sarcomatous changes (incidence around 0.29%).[3]

Despite its mostly asymptomatic and benign natural

history, it is the commonest indication of hysterectomy all over the world. The other surgical alternatives to conserve the reproductive potential of the women include myomectomy and uterine artery embolisation (UAE). These have significant health and economic impact. Debates are now being raised whether it is prudent to leave an asymptomatic leiomyoma untouched only watching it develop complications – menstrual, reproductive and mechanical or a combination of these, or start immediate management.[4]

Medical therapy, with the avoidance of unnecessary surgery is an attractive alternative option for leiomyoma management in modern gynaecology, but there is considerable variation in practice and uncertainty about most effective therapy. Currently, there are no definitive food and drug administration (FDA) approved agents for long-term medical treatment of uterine leiomyomata. Agents like gonadotropin-releasing hormone analogues (GnRHs), selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs), aromatase inhibitors(AIs), cabergoline, danazol and gestrinone, have been evaluated with varying degrees of success.[5,6]

Mifepristone, an antiprogesterone decreases myoma size and symptoms.[7,8] Various doses have been suggested mostly 10-20 mg daily. Higher doses does not increase the beneficial effect instead increase the side effects.[7] Low dose mifepristone has minimal side effects and is well tolerated.

Aim and objectives

Aim and objectives were to observe the effect of low dose m iferpristone (10 and 25 mg) on reduction of size of fibroids and relief of symptoms in woman of reproductive age group, and to find out any difference in response according to the size and type of fibroid.

METHODS

This was an institutional based prospective study conducted in the department of obstetrics and gynaecology of Calcutta national medical college and hospital, Kolkata, West Bengal; over a period of one and a half year (February 2019 to August 2020), after obtaining clearance from the institutional ethical committee. The study included 100 women of reproductive age group (according to inclusion and exclusion criteria) diagnosed with single uterine fibroid (on USG) attending OPD of our tertiary care hospital.An informed written consent was obtained from all the participants enrolled in the study.

Inclusion criteria

Non-pregnant women in reproductive age (25-45 years) without atypical endometrial hyperplasia were included in the study. Only single fibroid sized 1-6 cm were enrolled. In case of multiple fibroids, dimensions of the largest fibroids were taken were included I study.

Exclusion criteria

Pregnant females, women with severe anemia and with acute symptoms, presence of cervical or tubal diseases, current genital infections, fibroid size >6 cm, associated adenomyosis or endometriosis, endometrial hyperplasia with atypia on dilatation and curettage report, suspicion of leiomyosarcoma on USG, renal and hepatic dysfunction were not included in the study. Women with history of porphyria, history of breast or other genital malignancies, on hormonal medication and on corticosteroids in last three months of starting the treatment were also excluded.

On each visit, pictorial blood loss assessment chart (PBAC) score for menstrual bleeding, visual analog scale (VAS) score for pain symptoms, and any side effects (nausea, vomiting, weakness, fatigue, hot flushes) were assessed. Patients were followed up monthly till 3 months. USG for size and volume of fibroid, endometrial thickness (ET) and blood tests for Hb done before starting and after termination of treatment. Patients with fibroid size 1-2 cm (maximum diameter) were prescribed 10 mg mifepristone daily for 3 months and those with size between 2 to 6 cm (maximum diameter) were given 25 mg mifepristone daily for 3 months. Patients whose symptoms did not resolve/ developed any complication like severe anemia and aged around 45 years were planned for hysterectomy.

The results collected were tabulated and analysed. Statistical testing was conducted with the statistical package for the social science system version SPSS 20.0. Continuous variables were presented as mean with standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

A total of 100 cases of symptomatic uterine fibroid were recruited. Based on the maximum diameter of fibroid, they either received 10 mg or 25 mg of mifepristone daily for 3 months. Most of the women (41%) were between 36-40 years of age, followed by 29% aged 41-45 years, 24% were 30-35 years and 6% between 25-30 years. Majority of the patients (64%) were multipara, 27% were primipara and only 9% were nulliparous women. Predominant symptom in this study population was menorrhagia (84%), followed by heaviness in lower abdomen (42%), polymenorrhoea (36%), dysmenorrhea (18%), intermenstrual bleeding (12%), dyspareunia (5%) and infertility and dysuria both in 4%.

Before treatment, most of the women (83%) had PBAC score >100 and 17% had score <100. Forty one percent

women had VAS score 0-3, 42% between 3-5 and 17% had score >5. Most of them were anemic (44% had Hb between 7-9 g/dl, 42% between 9.1-11 g/dl) and 14 patients were non-anemic.

USG was done in all the cases. Intramural fibroid was most common type of fibroid (82%) followed by submucosal fibroid (18%). No subserosal fibroid was found during this study. The fibroid volume of <40 cc was found in 30% females, 57% between 40-80 cc and 13% between 80-120 cc. The endometrial thickness of 47% cases were <8 mm and 53% cases between 8-12 mm. Depending on the size the fibroid (maximum diameter of fibroid) 67 cases received 25mg and 33 cases received 10 mg mifepristone daily for 3 months. The mean values before and after treatment with the changes observed are shown in Table 1.

After 3 months of treatment, 87% patients developed amenorrhea, in 96% cases menstrual blood loss diminished, 51% cases abdominal pain subsided, polymenorrhoea resolved in 30 cases and in 11 cases symptoms did not subside. At the end of 3 months of mifepristone treatment, 76% cases had PBAC score of <100 and 24% cases had score >100. VAS score of <3 was seen in 66% cases, 29% had scores 3-5 and 5% had score of >5. In 54% cases Hb was 9.1-11 g/dl, 20% cases had Hb between 7-9 g/dl and in 26 % cases, it was >11g/dl.

After 3 months of treatment, fibroid volume was found to be <40 cc in 60% cases, 35% between 40-80 cc and 5% cases had fibroid volume between 80-120 cc. An increase of >12 mm in ET was observed in 22% cases, 37% cases had 8-12 mm of ET and <8 mm in 41% cases. Eleven patients (11%) had elevation in liver enzymes, 8% had nausea, 7% hot flushes, 10% leg cramps, 12% cases headache and 6% diarrhoea, whereas 82% patients had no side effects at the end of their treatment period.

Out of total 84 cases complaining of menorrhagia, 88.57% cases of intramural fibroid (62 out of 70) compared to 57.14% cases of submucosal fibroid (8 out of 14) showed relief in their symptoms. This differential response seen is statistically significant (p=0.013). Similar statistically significant differential response (p=0.001) between the two groups of fibroids was seen with respect to increase in Hb levels (Table 2).

Difference in response to treatment between intramural and submucosal fibroids with respect to pain abdomen and fibroid volume reduction was not found to be statistically significant (p=0.113 and 0.061 respectively) which can be attributed to the equal effect of mifepristone on all types of uterine fibroids as shown in Table 2.

Table 1: Effect of mifepristone after treatment for 3 months on the given parameters.

Parameters	Baseline (Mean)	After 3 months (Mean)	Changes in percentage (%)	P value
MBL by PBAC score	119.86±16.298	86.54±11.57	27.79 reduction	0.001
Severity of pain by VAS score	4.15±2.133	1.64±1.306	60.48 reduction	0.003
Hb (g /dl)	9.291±0.99	10.714±1.142	15.28 increase	0.002
Fibroid volume (cc)	63.428±24.86	43.536±17.23	31.36 reduction	0.001
Endometrial thickness (mm)	9.311±1.274	11.6±2.34	24.58 increase	0.002

Table 2: Comparison of mifepristone effect on intramural and submucosal fibroid.

Parameters		Intramural fibroid, n (%)	Submucosal fibroid, n (%)	Total	P value
Menorrhagia subsided after treatment?	Yes	62 (88.57)	8 (57.14)	70	0.013
	No	8 (11.42)	6 (42.85)	14	
	Total	70	14	84	
Pain subsided after treatment?	Yes	34 (80.95)	9 (56.25)	43	0.113
	No	8 (19.04)	7 (43.75)	15	
	Total	42	16	58	
Improvement of Hb % after treatment?	Yes	76 (92.68)	11 (61.11)	87	0.001
	No	6 (7.31)	7 (38.88)	13	
	Total	82	18	100	
Reduction of volume of fibroid after treatment?	Yes	75 (91.46)	13 (72.22)	88	0.061
	No	7 (8.53)	5 (27.77)	12	
	Total	82	18	100	

DISCUSSION

The management of uterine myomas depend on patient's symptoms, age and reproductive intentions. Due to its benign nature, the most conservative management should be considered to minimize morbidity, while improving the patient's outcome. Several clinical trials using 5-50 mg of mifepristone have been conducted over variable durations

between 3-12 months but the exact dosage and treatment duration are yet to be decided. We reviewed the peer articles on similar parameters i.e., MBL, pain abdomen, Hb levels and fibroid volume (Table 3).

The mean fibroid volume in our study was less when compared to other peer studies. This could be because fibroids of size 1-6 cm were included whereas in other studies the size of the fibroid included was of the higher range. Intramural was the most common type of fibroid in the present study which is comparable to the peer studies.

Endometrial hyperplasia (EH) is a significant unfavourable effect of mifepristone due to its antagonistic effect on the progesterone receptors, creating unopposed estrogenic environment.[9,10] The mean ET before treatment was found 9.31±1.27 mm, whereas after 3 months of treatment of mifepristone, the mean value increased to 11.6±2.34 mm. However, no cases of EH were reported during the study period. In the study conducted by Kapur et al 6% patients on 50 mg weekly mifepristone for 6 months developed complex EH without atypia, whereas Bagaria et al reported 63.1% cases of EH without atypia after 3 months of 10 mg daily mifepristone treatment.[11,12] Seth et al also observed that 2 out of 93 cases in their study developed simple EH.[13] Thus, keeping the duration of mifepristone treatment short can avoid chances of atypical EH and malignancy.

Patient compliance and acceptance for mifepristone as a medical management for symptomatic fibroids can be seen from the zero drop-out rate in our study. The major factors for this can be attributed to the low medicinal charges, no hospital admission, limited investigations, reduced need of blood transfusion and surgery, making this treatment modality really cost effective. Hysterectomy was planned only in 7 cases where symptoms persisted even after 3 months of Mifepristone treatment.

Table 3: Comparison of present study with the peer review articles.

Study name	Dose	Symptoms before treatment	Reduction of symptoms after treatment	Mean PBAC score	Mean VAS score	Mean Hb	Mean fibroid volume reduction
Present study	10/25 mg daily for 3 months	Menorrhagia 84%, heaviness in lower abdomen 42%	Amenorrhea 87%, decreased MBL 96%, abdominal pain subsided 51%	27.79% reduction (from 119.86-86.54)	60.48% reduction (from 4.15 to 1.64)	From 9.29 to 10.71 (15.28% increase)	31.36%
Kulshreshtha et al[8]	10/25 mg daily for 3 months	---	Amenorrhoea 96% (10 mg dose) and 90% (25mg dose)	From 253-19.8, from 289.2-10.4 with 10 and 25 mg resp.	Significant decrease in both groups ($p<0.01$)	---	36% and 22% with 10 and 25 mg resp.
Kapur et al[11]	50 mg/week for 6 months	Menorrhagia 89%, Pelvic pain 94.4%, backache 27.8%	Decreased MBL 100%, amenorrhoea 88.89%	Reduced from 111.70 to 7.12	---	Increased from 9.18-10.82 g/dl	44.57 %
Bagaria et al[12]	10 mg daily for 3 months	---	---	MBL index declined by 94.8%	---	17.8% increase (9.5-11.2 gm/dl)	26-32%
Seth et al[13]	25 mg for 3 months	---	---	---	---	raised to 137%	53.62%
Gupta et al[14]	25 mg daily for 3 months	AUB 94% menorrhagia 54%, polymenorrhoea 26%, menometrorrhagia 12%	Amenorrhoea 90%	---	---	---	---
Saharan et al[15]	10 mg daily for 3 months	Menorrhagia 82%, backache 72% pain abdomen 52%	Menorrhagia 48%, backache 20%, pain abdomen 20%	Reduced from 111.52 to 2.36	From 6.24-2.28 in 1st and from 6.24-1.18 in 3 months.	Raised by 27% at the end of 3rd month of treatment	From 91.13 cc to 38.73 cc
Sinha et al[16]	20-25 mg daily for 3 months	---	Menorrhagia 100% improvement, amenorrhoea 100%	---	>40% pain reduction in 90%, >80% pain reduction in 67.9%	---	---

Limitations of the current study can be attributed to the short study period, which masqueraded the long-term effects that mifepristone would have on the regressed as well as the new fibroids, and on other body parameters. As we did not have any case of subserosal fibroids in our study, the response of subserosal fibroids to mifepristone could not be studied.

CONCLUSION

Mifepristone is an effective and safe drug for the medical management of uterine myoma. Our results showed that Mifepristone (both 10 and 25 mg) led to symptomatic relief in patients, with 96% reduction in MBL and reversible amenorrhoea in 87% of the patients. Most of the literatures show that 25 mg dose of Mifepristone is superior to 10mg dose for larger fibroids. Our study showed that the intramural fibroid responded more to treatment than submucosal fibroid in terms of relief of menorrhagia and improvement of Hb concentration, although the size reduction is not significant in intramural as compared to submucous fibroid.

Mifepristone can be a suitable option especially in perimenopausal females in whom fibroids would regress after menopause and in nulliparous females who wish to avoid surgery. Even though its use as a primary medical therapy is limited due to chances of recurrence after treatment discontinuation, it can be used as an additional preoperative therapy, especially in cases of severe anaemia and larger fibroids where surgery is technically difficult or in unresectable cases. It does not cause major side effects, is tolerated well and is cost effective.

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

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