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Role of Low Dose Mifepristone on Uterine Leiomyoma in Reproductive Age Group: A Prospective Study

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Abstract

Aim: To study the effect of low dose mifepristone on the leiomyoma volume reduction, leiomyoma-related symptoms and endocrinal profile in patients with symptomatic leiomyoma. *Setting*: Tertiary care hospital *Material and Methods*: Sixty-two patients with symptomatic uterine leiomyoma were recruited and distributed to receive 10 mg mifepristone (Group 1) and placebo capsule containing 10 mg lactose (Group 2) OD for 3 months. Baseline leiomyoma-related symptoms and leiomyoma volume was recorded, followed by monthly assessment for three months. Baseline hormonal profile was done and repeated at the end of therapy. *Main outcome measure (s):* The reduction in the uterine leiomyoma volume, effect of mifepristone on the leiomyoma-related symptoms and the hormonal levels. *Result (s):* There was a significant percentual decrease (p = 0.000) in the total leiomyoma volume in the mifepristone-treated group, -58.36±8.92% (mean Â±S.D), compared with the control group, 0%. Mifepristone treatment significantly reduced the bleeding days (p = 0.000) by causing amenorrhea in all the patients (100%). There was a significant improvement in the leiomyoma-related symptoms and the hormonal levels remained unchanged. *Conclusion*: Mifepristone may offer an effective conservative treatment option for women with symptomatic uterine leiomyoma and the associated pronounced uterovaginal bleeding. It is efficacious in reducing leiomyoma volume and leiomyoma-related symptoms of menorrhagia and dysmenorrhoea.

Keywords: Mifepristone; Leiomyoma; Leiomyoma Volume; Leiomyoma Related Symptoms.

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Introduction

Leiomyomas are the most common benign tumors of the uterus and the female pelvis [1]. They are commonly encountered in 22-25 % of the women in the reproductive age group [2] and accounts for 30% of all hysterectomies [3]. Leiomyomas in majority remains asymptomatic and when symptomatic most common complaints were menstrual problems followed by a lump in the abdomen, lower abdominal pain, infertility and pressure symptoms [2]. The major concern of today is on cost containment, conversion of an abdominal procedure into less invasive vaginal or laparoscopic procedures. This interest towards minimally invasive surgery has led us to an era of hysterectomies, myomectomies and fibroid myolysis being performed by laparoscopic or hysteroscopic procedures. But the high cost, great expertise needed to perform them and the high incidence of complications limit their treatment potentials.

The availability of safe and effective non-surgical treatment of symptomatic leiomyoma would be of considerable clinical & public health importance. Till

now effective medical therapy that is likely to result in the permanent cure is still not available. Danazol causes a reduction in the leiomyoma volume but is associated with marked side effects (androgenic). GnRH analogs cause a significant reduction in leiomyoma size but again associated with many side effects as well as it is expensive also. Uterine artery embolization is a very effective non-surgical option but associated with asherman's syndrome and premature ovarian failure [1].

Mifepristone or RU486 is a selective progesterone receptor binding modulator with both anti-progesterone and anti-glucocorticoid activity. The primary effect of mifepristone is an antagonistic activity and both the endometrial and myometrial receptors are antagonized by mifepristone [4]. It causes a reduction in leiomyoma size by several mechanisms [5]. Multiple clinical trials have shown that the mifepristone in cases of leiomyoma causes leiomyoma volume reduction, improvement in the symptoms and the quality of life [6-10]. Mifepristone causes amenorrhoea in the patients as it inhibits or probably delays ovulation [1,3]. Other mechanisms suggested for decreasing the menstrual blood loss was the suppressive effect of mifepristone on the vasculature of the endometrium and it reduces the levels of vascular endothelial growth factor [11]. The present study was conducted to analyze the efficacy of low dose mifepristone for treating leiomyoma-related symptoms and effect of the drug on the leiomyoma size and endocrinal profile along with the side effects if any.

Material and Methods

The present study was conducted in the Obstetrics and Gynaecology department of the tertiary care hospital over a period of one year. It was a prospective interventional study. Ethical clearance was taken from the ethical committee of the concerned institute where the study was conducted. Sixty-two women with symptomatic uterine leiomyoma in the reproductive age group (20-35 years) were recruited from the Gynaecological OPD. Patients with the rapid growth or doubling of the size of the leiomyoma, any associated medical disorders (DM, HTN, Heart diseases or coagulation disorder), associated adnexal or ovarian mass, use of hormonal therapy, with profuse bleeding, the presence of pregnancy or lactation and histopathological evidence of endometrial hyperplasia were excluded. Written informed consent was taken from all the patients selected for the study.

Detailed history, examination and complete workup of the patients for leiomyoma including endometrial aspiration were done as per hospital protocols. History was taken regarding menstrual complaints and other leiomyoma-related symptoms. In the menstrual history quantification of the amount of blood loss was done based on pictorial blood loss assessment chart. For this standard pad were provided by the hospital. Score >100 was taken as menorrhagia i.e. >80 ml blood loss [2].

History of dysmenorrhoea, pelvic pressure, pelvic pain, low backache, rectal pressure, urinary frequency, dyspareunia and other symptoms were taken. The severity of the symptoms was graded according to the visual analog scale [7]. Thorough general and systemic examination was done with particular reference to the degree of pallor and presence of any contraindications to the study. Gynecological Examination was done to assess the size of the uterus and any other associated pathology. Ultrasound pelvis was done initially and repeated every month. Volume (cm3), location and number of leiomyoma were recorded on ultrasound examination. Basic investigations like Papanicolaou smear, hemoglobin level, LFT, and KFT were done. Endometrial biopsy was taken in premenstrual phase and patients with endometrial hyperplasia or any other abnormality were excluded. The hormonal assay was done on day 2 or 3 to know the baseline values (LH, FSH, Estradiol, TFT's, Testosterone and Cortisol). After the initial workup, a total of 62 patients with symptomatic fibroids were divided into two groups(32 in group 1 and 30 in group 2). Group 1 received cap mifepristone 10 mg and Group 2 received placebo (Cap lactose) once a day orally for 3 months. The drug was started after complete workup and excluding the contraindications for the study. Tablet mifepristone was prepared by the Sun Pharmaceuticals. They had placed the powdered form of the drug (10 mg) inside the capsules. The patients were blinded to the study as similar looking capsules were prepared for both the groups. All patients were followed monthly for a period of 3 months and the following parameters were noted like menstrual blood loss, the severity of leiomyoma-related symptoms, leiomyoma volume, the occurrence of any drug-associated side effects i.e. nausea, vomiting, diarrhea, headache, fatigue, hot flushes, and loss of libido. Repeat hormonal levels were done at the end of the therapy. Patients were followed up till three months post-resumption of menstruation. Primary outcomes were leiomyoma volume reduction and symptomatic improvement. Secondary outcomes were the effect on the endocrinal profile.

Data Analysis

Interventional versus placebo groups were compared by using various statistical methods. Unpaired t-test and Chi-square test were used to compare the baseline parameters between the two groups. The severity of symptoms between and within the groups, the % change in various symptoms score and ultrasound parameters at different points of time were evaluated by using ANOVA test. If on the comparison by ANOVA test the difference at different time points were found to be significant, the level of significance was determined by using Turkey's test at 5% level of significance. A p-value of <0.05 was taken as significant.

Observations and Results

Total 62 patients with symptomatic leiomyoma were recruited for the present study over a period of one year. Table 1. was showing the distribution of the patients in two groups. All the patients were evaluated at the end of the 1st, 2nd and 3rd month of the therapy. Reason for drop out cannot be commented as these two patients never reported back to the hospital. Both the groups were comparable with respect to various demographic parameters like age, educational status, socioeconomic class, and religion. Majority of patients in both the groups were between 30-34 years of age group, Hindu by religion and belong to the lower middle class.

Baseline parameters of both the groups were shown in table 2. Age group ranges from 20-35 years. Maximum patients in both the groups were multiparous, 62.5% (20/32) and 82.2% (23/28) in group 1 and 2 respectively.

Most of the patients presented with the menstrual complaints (65.62% & 64.3% in group 1 and 2 respectively), followed by other leiomyoma-related symptoms like dysmenorrhoea, pelvic pain, and dyspareunia. Among menstrual complaints, menorrhagia was the most common complaint. (52.38% and 39.3% in group 1 & 2 respectively) (Table 3).

Both the groups were comparable with respect to severity of symptoms, the number of leiomyoma, various biochemical parameters and hormonal levels.

The number of leiomyoma ranges from 33-36. 1.18±0.501 & 1.11±0.416 in group 1 and 2 respectively.

Leiomyoma volume was 56.61+19.74 cm3 and 52.13+13.97 cm3 in group 1 and 2 respectively. None of the patients had abnormal liver or kidney functions tests and abnormal hormonal levels at the time of recruitment, however, mean hemoglobin was <12gm% in both the groups with the mean value of 9.85+1.32.

Effect on menstrual bleeding and other leiomyoma-related symptoms

Cessation of menstruation was the most prominent finding in the mifepristone-treated group. 100% of the patients by the end of the first month and continuing through the end of 2nd and 3rd months versus none in the placebo group had a cessation of menstruation. This difference was highly significant at the end of every month (p-value: 0.00)

Reduction in the uterine bleeding and other leiomyoma-related symptoms were shown in Table 4. Significant numbers of women (80%) were relieved of dysmenorrhoea completely in mifepristone group while there was no change in the placebo group.

Table 1: Distribution of the patients in two groups

Groups	Total no. of patients recruited	Total no. Of patients completed the study	Drop out
GROUP 1 (Mifepristone)	32	32	-
GROUP 2 (Placebo)	30	28	2 (Dropout rate-6.66%)

Table 2: Baseline parameters of the study population

Baseline parameters	Group 1 (N=32)	Group 2 (N=28)
Age (years)	30.09±3.07	30.82±2.95
Parity	2.78±1.38	2.89±1.58
PBAC score	150.84±83.00	142.00±96.47
VAS	73.68±45.24	56.25±51.22
Leiomyoma volume (cm^3)	56.61+19.74	52.13+13.97
Haemoglobin level (gm/dl)	9.85±1.32	8.96±1.24

PBAC- Pictorial blood loss assessment chart, VAS score- Visual analogue scale score.

Effect on hemoglobin level and other biochemical parameters

Haemoglobin level increases after three months of mifepristone therapy. Variation in hemoglobin levels was shown in Table 5. There was 2.4 gm% increase in hemoglobin level which was the result of absolute amenorrhoea achieved within the first month of the therapy. This rise in hemoglobin level was significant with the p-value of 0.005.

No changes observed in other biochemical parameters after therapy

Effect on leiomyoma volume

Significant reduction in leiomyoma volume was observed in mifepristone group from 56.61cm3 to 23.59 cm3 (58.34% reduction) at the end of therapy compared to placebo group. A significant reduction was achieved at the end of the 1st month of therapy (26.13% reduction), which continued to decrease significantly in the 2nd and 3rd months (46.89% and 58.34% reduction respectively) in the mifepristone group (Table 6). Leiomyoma volume almost remained stationary in the placebo group. On comparing the two groups, it was observed that % reduction reached statistical significance at the end of each month with the maximum reduction at the end of 3rd month. When we compare % reduction between 2nd month & 1st month, 3rd month & 1st month and 3rd month & 2nd month, it was significant with the p-value 0.000.

Table 3: Showed population distribution on the basis of leiomyoma related symptoms

Symptoms	Group 1(Mifepristone) N=32 N (%)	Group 2 (Placebo) N=28 N (%)	P value
Menstural	21 (65.62)	18 (64.3)	
Menorrhagia	11 (52.38)	11 (39.3)	
Polymenorrhagia	5(23.80)	4(14.3)	0.675 (NS)
Polymenorrhoea	5 (23.80)	2 (7.1)	
Metrorrhagia	0 (0)	1 (3.6)	
Leiomyoma related symptoms	11 (34.37)	10 (35.7)	
Dysmenorrhea	5 (45.45)	5 (50)	
Pelvic pain	4 (36.36)	2 (20)	0.359 (NS)
Dyspareunia	2 (18.18)	3 (30)	

Table 4: Number of patients with complete resolution of symptoms after treatment

Symptoms	Group 1 (n=32) N (%)	Group 2 (n=28) N (%)	P value
Menstrual complaints	21/21 (100)	0/18 (0)	0.000 (S)
Dysmenorrhea	4/5 (80)	0/5 (0)	0.001 (S)
Pelvic pain	3/4 (75)	0/2 (0)	0.000 (S)
Dyspareunia	2/2 (100)	0/3 (0)	0.000 (S)

Table 5: Haemoglobin changes before and after treatment

Haemoglobin	Before treatment	After treatment	P value
Group 1	9.85±1.32 gm%	12.25± 3.42 gm%	0.005 (significant)
Group 2	8.96±1.24 gm%	8.74±1.04 gm%	NS

Table 6: Effect of mifepristone on the leiomyoma volume

Duration of therapy	Group 1 "Mifepristone" N=32 % change (Mean volume cm^3)	Turkey's test at 5% significance level	Group 2 "Placebo" N=28 % change (Mean volume cm^3)	Turkey's test at 5% significance level
Baseline	(56.61cm^3)	-	(52.13 cm^3)	-
1 Month	-26.13% (41.82 cm^3)	0.000 (S)	0 (52.13 cm3)	NS
2 Months	-46.89% (30.07 cm^3)	0.000 (S)	0 (52.13 cm3)	NS
3 Months	-58.34% (23.59 cm^3)	0.000 (S)	0 (52.13 cm3)	NS

Effect on hormonal profile and other side effects

On comparing both the groups no significant changes were observed in the mean hormonal levels at the end of the therapy. p-value is not significant.

Most common side effects observed were gastrointestinal intolerance, seen in 15 patients (46.87%), dry mouth in four patients (12.5%) and headache in 5 patients (15.62%). Rest of the patients had no side effect.

Post-treatment follow up

Patients were followed up till the resumption of menstruation. Surgical management was not required in any patients. Twelve patients had rebound growth in mifepristone group but it remained below the baseline volume.

Discussion

The present prospective study was conducted with the aim to study the efficacy of mifepristone in the reduction of leiomyoma volume, improvement in the leiomyoma-related symptoms and effect on the hormonal parameters.

Many investigators have studied the effect of mifepristone on the leiomyoma because of the fact that leiomyoma contains progesterone receptors. The first study demonstrating the decrease in uterine myoma volume in response to progesterone antagonist was done by Murphy et al. (1993) [12]. Many other clinical trials using Mifepristone in varying doses of 2.5 – 50 mg were done for variable periods of time (3-12 months) [3,13]. These studies showed a significant reduction of uterine volume and/or leiomyoma volume irrespective of the doses used.

Mifepristone is proved to be safe by multiple clinical trials and offers promise for three clinical uses – First, as an alternative to GnRH analog for use in pre-operative leiomyoma. Second, in perimenopausal women with symptomatic leiomyoma until menopause as leiomyoma typically regresses after menopause. Third, it can be used in younger women who wish to retain their fertility though its effect on fertility is unknown at present [3].

In the present study, 10 mg dose was chosen as various studies have shown that the dose as low as 10 mg is as effective as 25 mg & 50 mg and with the minimal side effects [3,13].

Cessation of menstruation was the most prominent finding in mifepristone group. 100% of the patients by the end of the first month continuing till the end of 2nd and 3rd months had a cessation of menstruation versus none in the placebo group. Several other authors have also reported amenorrhoea at the end of 3 months with doses ranging from 5mg to 50mg. Bagaria et al. [6] reported cessation of menstruation in 73.6% of the patients by the end of the first month and 84.2% of the patients at the end of 2nd and 3rd months versus none in the placebo group.Vidushi et al done one study comparing the effects of 10mg and 25 mg of mifepristone and found cessation of menstruation in 95.7% of patients at the end of 3 months with 10 mg dose [5]. Seema et al. showed amenorrhoea in 88% of patients with the same dose of mifepristone and duration of treatment. 14 Eisinger et al. [3] done the study with the prolonged duration of therapy by 6 and 12 months and they had reported amenorrhoea in 70% of patients. Thus, it seems that as the duration of treatment was increased, the prevalence of amenorrhoea was decreased.

In the present study, 80% of women were relieved of dysmenorrhoea completely in the mifepristone-treated group (4/5) versus none (0/5) in the placebo group, which was significant. (p-value 0.001) Bagaria et al. [6] used 10 mg mifepristone for three months and reported a significant decrease in the severity of dysmenorrhea and pelvic pain. Vidushi et al showed similar results (80% reduction) using same dose 10 mg of mifepristone for three months [5]. Eisinger et al. 2003 [3] used 10 mg of mifepristone for 6 months of duration and reported resolution of dysmenorrhoea in 41.6% of women which was lower than the reported literature and present study because it was observed that as the duration of therapy increases the menstruation resumes with associated dysmenorrhoea. Hangara et al. conducted a study using 50 mg mifepristone once weekly for 6 months and reported 83% reduction in dysmenorrhoea which is similar to our study, 67% in pelvic pain and 50% in dyspareunia cases [2].

Reduction in leiomyoma volume in the present study is 58.34% at the end of three months. Similar results were seen in the study conducted by Seema et al in 2016 with the same dose of mifepristone, 58% reduction at the end of 3 months [14]. Percentage reduction in the fibroid size in the different studies by Joseph Luis et al. [15] and Eisinger et al. [3] with the same dose of mifepristone) was 57% & 49%, respectively, results were similar to our study. Bagaria et al reported 32% of reduction with 10 mg

dose at the end of three months which is lower than our study [6]. In the present study, a significant difference from the placebo group was achieved at the end of each month.

In the present study, it was observed that hormonal parameters were within normal range in both the groups after three months of therapy and there was no effect of mifepristone on the hormones. However, Murphy et al. [16] reported that mifepristone increases the LH, androstenedione, and testosterone in first three weeks of treatment and then returned to baseline at fourth week without further changes during remainder of treatment but we were not able to observe this effect as in our study baseline hormones were measured and then at the end of the therapy, not monthly. In one study conducted by Engmann et al included thirty women and reported that serum cortisol levels remain unchanged in women treated with 50 mg of mifepristone which is similar to our finding [10]. This shows that normal physiology is maintained with the mifepristone therapy.

Most common side effects observed were gastrointestinal intolerance, seen in 15 patients (46.87%), dry mouth in four patients (12.5%) and headache in 5 patients (15.62%). Rest of the patients had no side effect. Meta-analysis of the previous studies reported hot flashes, joint pain, fatigue, dizziness, nervousness and loss of appetite in patients treated with mifepristone.

Hundred percent patients who attained amenorrhoea in the mifepristone-treated group, resumed menses within 26.16+1.43 days of cessation of the drug therapy. Bagaria et al reported resumption of menstruation within 10 weeks of cessation of the drug therapy [6].

There was only one study which assessed the long-term effects of low-dose mifepristone on myoma regression, symptoms and endometrial pathology [3]. This study also assessed the regrowth of myomas after cessation of therapy. Nine women were followed post-therapy, in most of the cases uterine volume increased but remained on an average 42% less than the baseline. In the present study, follow-up post-resumption of menstruation of 27 out of 32 patients were available. In three out of 27 patients rebound growth occurred. In patients who had rebound growth, the leiomyoma volume remained on an average less than 50% of the baseline. Yang et al. x reported that 20 women had no measurable change in leiomyoma size, 3-9 months after completion of mifepristone treatment [17].

Conclusion

It was concluded from the study that the three months therapy with 10 mg of mifepristone is the efficacious, acceptable, safe and non-surgical treatment of symptomatic fibroids. However, larger multicentric trials are recommended to determine the safety, ideal dosage and duration of the therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgment

Nil

Ethical Approval

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed Consent

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

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