Original Article

Mifepristone in Fibroids: Comparative Study of Safety and Efficacy of Biweekly Dosage Vs Daily Dosage Schedule

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Abstract

Background: Leiomyomas are the most prevalent benign tumors of the uterus and are seen more with increasing age. 50 mg biweekly dose was compared with 25 mg daily dose in terms of efficacy and safety in symptomatic women as the biweekly dose maybe an economically better alternative. Two different dosages of mifepristone for medical management of fibroids were compared in terms of efficacy and safety in symptomatic women. **Materials and Methods:** Ninety-two women were recruited who fulfilled the criteria after informed consent and were randomized in two groups. Sample size was calculated on the basis of earlier literature, for response in terms of reduction in fibroid volume, assuming 1% level of significance and 95 % power of study, the optimum sample size came out to be minimum 27 in each group. Assuming loss to follow up of few patients, we took 45 patients in group 1 and 47 patients in group 2. Group 1 was given mifepristone in a dose of 25 mg once a day and Group 2 was given mifepristone 50 mg biweekly for 3 months. Fibroid volume, uterine volume, endometrial thickness, pictorial blood loss assessment chart score, hemoglobin levels, and liver transaminases were recorded at the beginning and at the end of treatment. Side effects were noted at the end of the treatment. **Results:** Both the dosages lead to improvement in symptoms of the patients. Mifepristone significantly reduced fibroid volume in both the groups, but the difference between the groups was not significant ($P = 0.99$). Mifepristone treatment significantly reduced bleeding and increased hemoglobin levels in both the groups. The side effects were mild and tolerable. **Conclusion:** Mifepristone in both dosages is highly efficacious in causing amenorrhea, improving anemia, and enhancing the quality of life, and hence 50 mg biweekly dosage shows potential for being cost efficient.

Keywords: *Biweekly, comparison, fibroids, mifepristone*

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Introduction

Fibroids are the most common benign tumor, reported to occur in about 70% of women in their reproductive years and about 40% have symptoms severe enough to warrant therapy.[1] The definitive treatment, so far, has been surgical and sums up to 40% of all hysterectomies in premenopausal women. Myomectomy is an alternative for patients desiring child bearing. Application of medical treatments is limited to reduction of related symptoms preoperatively, correction of anemia and size reduction. Uterine artery embolization carries potential risk of premature ovarian failure and has its own risks, limitations, and availability is an issue. The drugs most commonly used are gonadotropin-releasing hormone (GnRH) agonist and selective progesterone receptor modulator (SPRM).[2] GnRH agonist reduces leiomyoma size to about 50% in 3 months, but, it is expensive, and has to be given parenterally. Also long term use of GnRH agonists treatment is accompanied by significant side effects such as hot flushes, night sweats, bone resorption due to hypoestrogenic effect, etc. Cessation of GnRH causes regrowth of myoma and recurrence of symptoms. The levonorgestrel intrauterine device is effective in reducing menstrual blood loss and restoring hemoglobin

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levels, and it can be an alternative to surgical treatment. Although the expulsion rate of levonorgestrel intrauterine device is high in patients with fibroid uterus. When cavity size is big, its not seen to be successful and it has no effect on the size of uterine myoma. Of the SPRMs, there is good supportive literature for the use of ulipristal. However ulipristal is an expensive option and maybe out of reach of the general population. Mifepristone has also been found to be effective in reducing the size of fibroid and maybe a more cost efficient substitute of considerable public health importance. Using biweekly dosage schedule further cuts down the cost remarkably by 40-50 %. This study, comparing the two dosages, has been carried out for the first time and it has the potential to make a noteworthy public health impact. We took the study because if safety and efficacy is same, biweekly dose is cost efficient and will have potential for greater use in all resource poor third world country like ours.

Materials and Methods

The present randomised controlled trial was conducted on an outpatient basis. Ninety-two patients with symptomatic fibroids were randomized into Group 1 and Group 2, using computer-generated random number tables, receiving 25 mg once a day (OD) and 50 mg biweekly mifepristone orally for 3 months, respectively. Inclusion criteria defined were symptomatic fibroid cases measuring at least 3 cm in the smallest dimension exhibiting heavy menstrual bleeding or dysmenorrhea or pelvic pressure, those giving consent, accepting the use of nonhormonal contraceptives, and willing for endometrial biopsy if required. Exclusion criteria defined were patients who were planning pregnancy, breastfeeding, menopausal, with coagulopathies, with severe anemia, and <5 g/dl hemoglobin, used corticosteroids or mifepristone in the past 3 months, used GnRH analogs in the past 6 months, any history of suspicion of any malignancy or hematological, renal, or hepatic dysfunction were excluded.

After enrolment, all patients were subjected to detailed history pertaining to fibroid-related symptoms such as menorrhagia, dysmenorrhea, nonmenstrual abdominal pain, dyspareunia, low backache, urinary frequency, rectal pressure, pelvic pressure, and low backache. Severity of symptoms was graded according to 10-point visual analogue scale (VAS), while quantification of blood loss was done using pictorial blood loss assessment chart (PBAC).[3,4] A score of 100 or more amounts to menorrhagia. Blood samples were collected for investigations including complete hemogram and baseline liver transaminases.

Complete gynecological examination and a detailed baseline pelvic (abdominal or vaginal) ultrasound was done to know the exact size and volume of uterus, number, size, volume and location of fibroids, and endometrial thickness at the start of treatment. Three largest diameters (A, B, and C) were measured in two planes in approximately perpendicular axis in all fibroids. The volume was calculated using formula for an ellipsoid, $0.523 \times A \times B \times C$. In case of multiple myoma, largest one (dominant) was used for volume calculations and its variations were used to evaluate effectiveness. All ultrasonography data were obtained by multiple doctors specializing in ultrasound. Calibrations taken at the two stages of study were performed by sonographers blind to previous measurements and knowing only the location of the fibroid to be measured, in case the subject had more than one such fibroid. Location was provided so that the particular fibroid we were focusing on was analyzed particularly carefully though all fibroids were noted along with the size of the uterus.

Endometrial biopsy was performed before treatment if any of the following criteria applied (a) endometrial thickness >8 mm, (b) episodes of vaginal bleeding more than 8 days, (c) vaginal bleeding during the 3 weeks before onset of menstruation, (d) in all subjects with family history or high-risk factors for carcinoma endometrium.

Mifepristone is now commercially available in India as a 25 mg tablet. After screening, qualified subjects were randomized into two treatment groups.

- Group 1: 25 mg mifepristone group: starting from day 1 to 3 of the menstrual cycle, 25 mg tablet of mifepristone to be taken orally every day for 3 months
- Group 2: 50 mg biweekly mifepristone group: starting from day 1 to 3 of the menstrual cycle, two 25 mg tablets of mifepristone to be taken orally twice a week on the same days for 3 months (Monday–Thursday or Tuesday–Friday or Wednesday–Saturday).

Following outcome measures were compared pre- and post-treatment:

1. Volume of fibroid, uterine volume, and endometrial thickness
2. Change in hemoglobin levels
3. Pattern of periods by PBAC charts
4. Fibroid symptomatology before and after treatment based on VAS
   a. Dysmenorrhea
   b. Nonmenstrual abdominal pain
   c. Dyspareunia.

   Note was made regarding pelvic pressure, low backache, and urinary symptoms
5. Laboratory data including liver function tests

6. Side effects if any in the form of nausea, vomiting, diarrhea, abdominal pain, hot flushes, fatigue, and irregular bleeding
7. Endometrial biopsy (if performed).

Statistical analysis and ethical consideration

Response rates in terms of increase in proportion of cases showing reduction in fibroid volume and amenorrhea, normal test of proportions was applied. For testing significance of association, "Chi-square" test was used. Quantitative outcome was compared using Student's *t*-test/Mann–Whitney test. Data analysis was performed using Statistical Packages for the Social Sciences (SPSS Inc., Chicago, IL, USA, version 25.0 for windows). The study was conducted among the patients coming to the outpatient department of Department of Obstetrics and Gynaecology of Government Medical College and Hospital, Chandigarh, after obtaining ethical clearance from the institute's ethics committee. This study was conducted on ethical guidelines for biomedical research on human subject as given in the "Declaration of Helsinki." The study was registered in Clinical Trial Registry of India (CTRI/2018/06/014616). A written and informed consent was obtained from all.

Results

Demography of all 92 women is depicted in Table 1. The mean (SD) age was 40.3 (5.6) and 41.4 (6) in group 1 and group 2, respectively. Most of the women in both the groups were para 2 followed by para 3. Only 1 women in group 1 was nulligravida and unmarried. There was no significant difference in age, parity and duration of symptoms in both the groups.

Effect of treatment on fibroid volume and uterine volume

The median (Q1, Q3) volume (cm3) of the fibroid at baseline was 97.5 (68.5, 174.6) in group one and 101.6 (82.3, 157.1) in group two. The difference was not significant. The volume of the fibroid changed from baseline to the end of three months in group one median (Q1, Q3) from 97.5 (68.5,174.6) to 75.3 (55.2,136.5) and in group two from 101.6 (82.3,157.1) to 82.7 (65.4,122.6) and was significantly reduced in both the groups (P <0.05). The percentual decrease in volume of the fibroid was normally distributed with a skewness <±1 and therefore permitted us to analyze by means within a 95% confidence interval (CI). The percentual decrease in fibroid volume was significant in both the groups that gave a reduction of mean within 95% CI −21.7 -19.5 % to -23.3 % in Group 1 and in Group 2; the mean within 95% CI decrease in fibroid volume was −19.7 -16.1 % to -21.5 %. The % decrease in Fibroid volume between groups was not significant (P=0.99). The P value for percentage decrease in fibroid volume between Group 1 and Group 2 was 0.985 and was not found to be significant at 95% CI.

Normal test of proportions was applied and it was found that the uterine volume (cm3) was reduced in group one median (Q1, Q3) from 240.7(180.6, 324.8) to 198.3(143.3, 245.2) which was significant. Within group two also a significant reduction from baseline 189 (149.8, 303.5) to 156.3 (120.6, 265.8) by the end of the study was observed. There was significant decrease (P <0.001) in the percentual uterine volume from baseline to the end of the study in both the groups (mean within 95% CI) was -18.5 (-13.5 to -20.2) % in group one and - 15.7% (-12.9 to -18.9) in group two. The % decrease in uterine volume between groups was not significant (P=0.34) [Table 2].

Effect of mifepristone on both groups according to volume and size of largest fibroid

Fibroids were divided in to three groups according to the volume and size of largest fibroid as being ≤5 cm in greatest dimension, ≤10 cm and >10 cm, to see if there was any difference in the action of mifepristone according to size of fibroid. There was no significant difference in percentage decrease in volume of fibroid as per size.

Effect of mifepristone according to type of fibroid on both the groups

Effect of mifepristone was studied according to the type of fibroids, most common in our study being intramural followed by submucosal and subserosal. None of the patients has subserosal fibroid in 50 mg group. At the end of the study, there was no significant difference in percentage decrease in volume of fibroid according to type of fibroid, in both the groups.

Effect of mifepristone on pictorial blood loss assessment chart score

PBAC reduced significantly from baseline to 3 months therapy in both groups (P < 0.001) and the effect started

Table 1: Demographic characteristics of randomised patients

Demographic characteristics	Group 1 Mifepristone 25 mg OD	Group 2 Mifepristone 50 mg Biweekly
Age (years) (mean±SD)	40.3±5.6	41.4±6
Parity (median IQR)		.
Nulliparous	0	1
Para 1	1	5
Para 2	31	24
Para 3	12	15
Para 4	1	2
Duration of symptom (Mean±SD) (Months)	13.6±12	14.2±18

at the very first cycle. PBAC scores at the beginning and at the end of treatment are shown in Table 2. Reduction in median PBAC score was significant in group one and group two, median (Q1, Q3) being 224(167-342) to 0 and 239 (158-308.5) to 0, respectively. With mifepristone, 44 out of 45 (97.8%) in Group 1 and 46 out of 47 (97.9%) in Group 2 developed amenorrhea.

There was no significant difference between the effects of mifepristone on PBAC score at both the dosages ($P = 0.914$) [Table 2].

Effect of mifepristone on hemoglobin levels

At baseline, there was no significant difference in blood hemoglobin levels (mean ± standard deviation) of both the groups (9.2 ± 1.7 g/dl vs. 9.2 ± 1.4 g/dl). Hemoglobin levels increased significantly from 9.2 ± 1.7 g/dl to 10.7 ± 1.3 g/dl in Group 1 and from 9.2 ± 1.4 g/dl to 10.8 ± 1.2 g/dl in Group 2. There was significant rise in hemoglobin in both the groups with treatment, but there was no significant difference in increase in hemoglobin between the groups ($P = 0.799$) [Table 2].

Effect of mifepristone on haemoglobin levels was also compared according to severity of anemia. Patients were divided into no anemia, mild anemia, moderate anemia, and severe anemia according to the World Health Organization classification of 2011 for nonpregnant females. There was no significant difference on comparing increase in hemoglobin according to type of anemia.

Effect of mifepristone on Visual Analog Scale score of symptoms

Visual Analog Scale score for dysmenorrhea

Thirty-nine (86.7%) patients in Group 1 and 41 (87.2%) patients in Group 2 presented with dysmenorrhea. There was marked relief with significant decrease in VAS score in both groups with therapy ($P < 0.05$) [Table 3].

Visual Analog Scale score for nonmenstrual abdominal pain

Nonmenstrual abdominal pain was present in 5 (11.1%) patients in Group 1 and 2 (4.2%) patients in Group 2, which was significantly relieved in Group 1.

Visual Analog Scale score for dyspareunia

Eleven (20%) patients in Group 1 and 10 (21.3%) patients in Group 2 presented with dyspareunia which also decreased significantly ($P < 0.05$) in both groups.

Three patients in Group 1 and 3 in Group 2 presented with low backache, which was relieved at the end of treatment.

Parameters to compare the safety of different dosages

1. Liver transaminases: No significant changes were noted in the liver transferase enzyme profile in both the groups.

At the end of 3-month therapy in both the groups, there was no significant increase in endometrial thickness.

Premenstrual endometrial aspiration biopsy was performed in 18 patients in Group 1, and six patients in Group 2 at beginning of the treatment. However, all the endometrial biopsies were reported to be as secretory phase. None of the biopsies show any complex hyperplasia or atypia in either group.

Table 2: Effect of different dosage schedules of mifepristone on Fibroid, Uterine volume, PBAC score and hemoglobin levels

Parameter (cm^3)	Group 1 *n*=45			Group 2 *n*=47		
	baseline	At 3 months	Sig. P	baseline	At 3 months	Sig. P
Fibroid volume Median (Q1, Q3)	97.5 (68.5,174.6)	75.3 (55.2,136.5)	<0.001a	101.6 (82.3,157.1)	82.7 (65.4,122.6)	<0.001[a]
% change		21.7% (19.5-23.3)			19.7% (16.1-21.5)	0.98b
Uterine volume Median (Q1, Q3)	240.7 (180.6,324.8)	198.3 (143.3,245.2)	<0.001a	189 (149.8,303.5	156.3 (120.6,265.8)	<0.001[a]
% change		18.5%(13.5-20.2)			15.7% (12.9-18.9)	0.34b
PBAC score Median (Q1, Q3)	224 (167,342)	0 (0)		239 (158,308.5)	0 (0)	0.91
Haemoglobin Mean±SD (g/dl)	9.2±1.7	10.7±1.3		9.2±1.4	10.8±1.2	0.79

n is the number of participants in each group. Group 1 received 25 mg once a day and group 2 received 50 mg biweekly for three months. The percentual change (%) was distributed with skewness less than±1 permitting means within 95% confidence interval. [a]*P* - value within group between baseline and end of study. [b]*P* - value between groups at the end of study. PBAC, Pictorial Blood loss Assessment Score

Table 3: Effect of different dosage schedules of mifepristone on 10- point VAS score for dysmenorrhoea

VAS score	Group 1 *n*=45	At 3 months	Group 2 *n*=47	At 3 months
No pain (0)	6 (13.3%)	44 (97.8%)	6 (12.8%)	47 (100%)
Mild pain (1-3)	1 (2.2%)	1 (2.2%)	1 (2.1%)	0 (0%)
Moderate pain (4-6)	22 (48.9%)	0 (0%)	20 (42.5%)	0 (0%)
Severe pain (7-10)	16 (35.5%)	0 (0%)	20 (42.5%)	0 (0%)

n, number of participants in each group.

Table 4: Effect of mifepristone on various parameters in previous studies with similar dosage

Authors	No Of patients	Dose of drug	Treatment duration (months)	% reduction in fibroid volume	% reduction in uterine volume	% of patients Developing amenorrhoea	Hb before treatment	Hb after treatment
M. Engman *et al* (2009) [16]	15	50 mg thrice a week	3	34	0	100		
Mukherji *et al* (2011) [17]	30	25 mg per day	6	-	160 ml	75.7		
Kulshreshtha *et al* (2013) [8]	73	25 mg per day	3	24		95.7	10.9±1.8	11.7±1.3
Shikha seth *et al* (2013) [18]	93	25 mg per day	3	46	36.3	92.68	8.9±2.1	11.8±1.3 Increased by 2.8±1.5
Rani BS *et al* (2016) [19]	40	25 mg per day	3	43.84	38.8%	100	8.6±0.8	10.1±1.0
Arora *et al* (2017) [14]	60	50 mg biweekly	6	36.9-39.4		100	9.66	10.09 at 3 months
Chongdong liu *et al* (2017)[20]	96	25 mg per day	3	42.59	-			
Anupama Hari *et al*. (2017)[21]	50	25 mg per day	3	51.2%	34.3	86	9.9±1.1	11.3±1.1 Increased by 13.9%
Alaknanda *et al*. (2019) [15]	50	25 mg per day	3	30.69	17.39	84.6	9.96±1.2	10.9±0.8 Increased by8.5%

Hb , Hemoglobin

2. Side effects

The side effects were minimal, included nausea in 3 (6.7%) and 2 (4.2%), vomiting in 1 (2.2%) and 1 (2.1%), hot flushes in 2 (4.4%) and 3 (6.3%), fatigue in 2 (4.4%) and none, and diarrhea in 1 (2.2%) and none of the patients in Group 1 and 2, respectively. None of the patients complained of abdominal pain or irregular bleeding.

Discussion

SPRMs have shown promise for treatment of women with fibroids. The class of SPRMs includes various drugs such as mifepristone, ulipristal acetate (UPA), and asoprisnil.

Multicenter clinical trials labeled as "PEARL I–IV" have been carried out to prove the efficacy and safety of UPA in the medical management of leiomyomas. In the first trial, treatment with 5 and 10 mg UPA resulted in amenorrhea in 70% of patients and hemoglobin levels increased by 4.2 g/dl along with iron supplementation of 80 mg/day, and 12%–21% decrease in fibroid volume was observed. In PEARL IV on-and-off four 12-week courses of UPA were given, each treatment course separated by a drug-free period of two spontaneous menstrual bleeds, resulted in amenorrhea in 70%–74% patients, and a 65%−67% reduction in fibroid volume was observed from baseline.[5]

In the review done by Gurusamy *et al*. in 2016, mifepristone was found to cause significantly higher hemoglobin levels than leuprolide.[6]

Mifepristone is a SPRM and was initially studied by Murphy and Castellano in 1994 as a treatment option for fibroid.[7] Various studies have been done in India and internationally since then, to study the effect of mifepristone in different doses, starting from 2.5 mg OD and up to 50 mg OD and lasting for a duration of 3 months to a year.[7-12]

Using twice weekly has the rationale that mifepristone has a half-life of 26–48 h and high levels can be maintained in blood up to 72 h, and doing so may prove to be as beneficial as a daily dose.[13] Also Arora *et al*. in 2017 showed that biweekly 50 mg mifepristone decreases the size of fibroid by about 36-39 % over a duration of six months.[14] A biweekly dosage schedule is more cost efficient and becomes an affordable option to many patients with good safety profile. This is the first study to compare the efficacy and safety of 25 mg OD dose with biweekly 50 mg dose over a three months period.

UPA is available in India at a cost of □110 to 140 per tablet approximately given in a dosage of five mg per day. A single course of three month amounts to an average cost of □12000, which is expensive, especially for a low resourced developing country like ours and therefore, stays largely unaffordable. Mifepristone is now being marketed in India as 25 mg tablet, costing approximately □ 40–50/tablet. Hence, a 3-month course costs the patient about □3600–4500. The biweekly dosage will further cut down the cost to □1920–2400 for a 3-month course, inspire patient's compliance, and may further reduce the side effect. In a developing country like ours, we need medical treatment that is affordable to the entire population.

Table 5: Side effects as seen in previous studies with similar dosages of mifepristone

Authors	No Of patients	Dose of drug	Treatment duration (months)	Side effects
Present study	45	25 mg per day	3	Nausea- 6.7% Vomiting- 2.2% Hot flushes- 4.4% Fatigue-4.4% Diarrhoea-2.2%
	47	50 mg biweekly	3	Nausea -4.2% Vomiting-2.1% Hot flushes-6.4%
Kulshreshtha *et al* (2013) [8]	73	25 mg per day	3	Leg cramps -10% Hot flushes 7.1% Weakness 7.1% Palpitations 1.4% Headache 4.1% Allergic reaction -1 patient.
Shikha seth *et al* (2013) [18]	93	25 mg per day	3	Headache -12% Hot flushes 3.65%
Rani BS *et al* (2016) [19]	40	25 mg per day	3	Fatigue- 6 patients
Arora *et al* (2017) [14]	60	50 mg biweekly	6	10% (hair fall, headache, puffiness of body)
Chongdong liu *et al* (2017) [20]	96	25 mg per day	3	treatment related adverse events (hot flashes, mood changes, sweating, vaginal dryness)-17%
Anupama Hari *et al*. (2017)[21]	50	25 mg per day	3	Nausea 8% Pain abdomen 8% Hot flushes 6%
Alaknanda *et al*. (2019)[15]	50	25 mg per day	3	Nausea 12% Backache and hot flushes -6%

The main role of mifepristone is in controlling heavy menstrual bleeding, for symptomatic women, presurgery, so that their blood haemoglobin levels are improved, and in enhancing their general well-being. This drug has also been proved to be a pharmacological adjunct in premenopausal females with symptomatic fibroids, in whom we know the fibroids will regress postmenopause and in order to consume the few months or years that stand in perimenopausal period. Also by reducing the size of fibroid, it may become amenable to minimally invasive surgery.

Reduction in fibroid volume in 25- and 50- mg mifepristone groups was found to be 21.7 % and 19.7 %, respectively. Similar result was reported by Kulshrestha *et al*. with 25 mg dose, a 24% reduction in myoma volume, other studies have documented a reduction in volume ranging from 24% to 80% [Table 4].[8]

Significant reduction of uterine volume was also noted in both the 25- and 50- mg mifepristone groups (18.5 % and 15.7%, respectively). Similar reduction of 17% has been reported with 25 mg dose in study by Alakananda *et al*.; however, a range of 17%–38% has been reported in other studies [Table 4].[15]

There are few limitations of the present study. We had no follow-up data of the patients having relapses or nature of menstrual cycle posttreatment. Duration of treatment was 3 months; hence, more studies are required on the long-term benefits and repeat courses of mifepristone treatment. Iron therapy was not monitored and stringent control of iron intake could have augmented hemoglobin correction.

In current study, mifepristone 25 mg OD and 50 mg biweekly both dosing schedules are causing amenorrhea in around 97% of patients and increasing hemoglobin by 1.5 g/dl. Both dosages showed a 19.7%–21.7% fall in fibroid size which is less than reported in previous studies but were effective in relieving the patient of her symptoms, thereby improving her general well-being and giving time for building up the patient's anemia without the need of blood transfusion. Very few patients had side effects and they were tolerable such as nausea, hot flushes, vomiting, and diarrhea which are similar to previous studies as shown in Table 5. These results are similar to PEARL I study, in which UPA 5 and 10 mg OD was administered for 3 months, and 12%–21% decrease in fibroid volume was observed and which

further increased to 65%–67% with four courses of 3 months.[5]

All subjects were compliant very well with the biweekly dosage. They were told to mark their days on a calendar to ensure good compliance. Biweekly dosage may be forgotten in comparison to daily dose, but in our study, due to the short period of administration and specifically with the biweekly dosage group compliance was observed to be good, due to the significant control in abnormal uterine bleeding.

We conclude that 50 mg biweekly dosage is not only efficacious but it has a good safety profile, is exceedingly cost- productive alternative to 25 mg OD dose in respect to causing amenorrhoea, decreasing fibroid volume and uterine volume, and improving haemoglobin. However, further studies are required to establish the long term efficacy and safety, chiefly for anemic and premenopausal females with symptomatic leiomyomas in whom this drug can be highly suitable, in terms of lowering cost, buying time for surgery, improving anemia, and maybe avoiding surgery altogether. More studies are required to establish the efficacy and safety of repeated courses of mifepristone.

Conclusion

Current study of 92 patients divided into 25 mg daily mifepristone and 50 mg biweekly mifepristone for three months suggests that the later shows greater potential for vaster clinical use. It can be a more appropriate alternative for patients in terms of compliance, ease of intake as it can be taken biweekly, rather than daily, is more cost effective. A three month course of biweekly dosage schedule gives a saving of approximately □ 1500-2000 to the patient that is about 40-50% economical and is of considerable importance to a majority of our low-income population and has a similar outcome in terms of efficacy as well as safety when administered for three months. Prospectively, it can have a notable public health impact in a third world country like ours.

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Conflicts of interest

There are no conflicts of interest.

References

1. Tropeano G, Amoroso S, Scambia G. Non-surgical management of uterine fibroids. Hum Reprod Update 2008;14:259-74.
2. Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev 2017;11:CD000547.
3. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: How to choose a scale? Hum Reprod Update 2015;21:136-52.
4. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990;97:734-9.
5. Powell M, Dutta D. Esmya® and the PEARL studies: A review. Womens Health (Lond) 2016;12:544-8.
6. Gurusamy KS, Vaughan J, Fraser IS, Best LM, Richards T. Medical therapies for uterine fibroids – A systematic review and network meta-analysis of randomised controlled trials. PLoS One 2016;11:e0149631.
7. Murphy AA, Castellano PZ. RU486: Pharmacology and potential use in the treatment of endometriosis and leiomyomata uteri. Curr Opin Obstet Gynecol 1994;6:269-78.
8. Kulshrestha V, Kriplani A, Agarwal N, Sareen N, Garg P, Hari S, *et al*. Low dose mifepristone in medical management of uterine leiomyoma – An experience from a tertiary care hospital from north India. Indian J Med Res 2013;137:1154-62.
9. Carbonell Esteve JL, Riverón AM, Cano M, Ortiz AI, Valle A, Texidó CS, *et al*. Mifepristone 2.5 mg versus 5 mg daily in the treatment of leiomyoma before surgery. Int J Womens Health 2012;4:75-84.
10. Hangarga US, Rita D. Low dose mifepristone in the treatment of uterine leiomyoma. Int J Reprod Contracept Obstet Gynecol 2016;6:44-8.
11. Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. J Minim Invasive Gynecol 2005;12:227-33.
12. Carbonell JL, Acosta R, Pérez Y, Garcés R, Sánchez C, Tomasi G. Treatment of uterine myoma with 2.5 or 5 mg mifepristone daily during 3 months with 9 months posttreatment followup: Randomized clinical trial. ISRN Obstet Gynecol 2013;2013:doi. 10.1155/2013/649030.
13. Sarkar NN. Mifepristone: Bioavailability, pharmacokinetics and use-effectiveness. Eur J Obstet Gynecol Reprod Biol 2002;101:113-20.
14. Arora D, Chawla J, Kochar SPS, Sharma JC. A randomized control trial to assess efficacy of Mifepristone in medical management of uterine fibroid. Med J Armed Forces India 2017;73:267-73.
15. Seth S, Goel N, Singh E, Mathur AS, Gupta G. Effect of mifepristone (25 mg) in treatment of uterine myoma in perimenopausal woman. J Midlife Health 2013;4:22-6.
16. Rani BS, Kumari PD, Usha P. Effect of low dose mifepristone in symptomatic uterine fibroids. J Evid Based Med Healthc 2016;3:909-13.
17. Liu C, Lu Q, Qu H, Geng L, Bian M, Huang M, *et al*. Different dosages of mifepristone versus enantone to treat uterine fibroids: A multicenter randomized controlled trial. Medicine (Baltimore) 2017;96:e6124.
18. Sruhya M, Hari A. A prospective and interventional study of the role of low dose mifepristone in the management of uterine leiomyoma in perimenopausal women. Saudi J Med Pharm Sci 2017;3:1088-96.
19. Alakananda D, Basumatary DB, Reddy DBS. Mifepristone In The Medical Management Of Uterine Fibroids. Indian Journal Of Applied Research 2019.
20. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell-Danielsson K. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Hum Reprod 2009;24:1870-9.
21. Mukherjee S, Chakraborty S. A study evaluating the effect of mifepristone (RU-486) for the treatment of leiomyomata uteri. Niger Med J 2011;52:150-2.