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Low dose mifepristone in the conservative management of leiomyomas: A prospective randomised controlled trial

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Abstract
Background: Leiomyoma is the most common benign tumour of uterus occurring in up to 20% of women with maximum incidence between 35-45 years of age leading to menorrhagia, pain and lump in abdomen. Incidence increases with age during the reproductive years such that cases occur in 20% to 50% of women older than 30 years. By extrapolation of findings from a prospective histopathology study of 100 consecutive total hysterectomy specimens, the prevalence of uterine fibroids in the general female population may be as high as 80% and is unchanged by menopausal status.
Aim of the Study
1. To find the effectiveness of Mifepristone in the medical management of uterine leiomyomas.
2. To compare the dose response effect in the form of assessing the change in symptomatic profile and regression in volume of the fibroids. The present study compares the effect of 25 mg and 50 mg Mifepristone (administered once weekly for 6 months).

Materials and Methods: The present study was carried out as a prospective randomized controlled trial comparing the dose response effects of 25 mg and 50 mg weekly administrations of Mifepristone for 6 months. 100 patients satisfying the inclusion criteria were selected for the study. Mifepristone is available as 200 mg tablet (25 mg= $1/8^{th}$ of the tablet & 50 mg = $1/4^{th}$ of the tablet).
Results: Myoma volume (6 months) groups table depicts the classification of subjects by myoma volume at 6 months. It is evident from the result that 86.00% subjects were in the ≤ 100 cm3 group followed by 14.00% subjects in 101-150 cm3 group in MIF 25 group. Similarly in MIF 50 group 100.00% subjects were in the ≤ 100 cm3 group (p= <0.0001, unpaired t test)
Conclusion: When symptomatic profile and regression in volume of the fibroids were matched, the following conclusions was observed in MIF 50 treatment compared to MIF 25 treatment
- Better reduction in menstrual blood loss
- Higher reduction in pain

Enhanced reduction in myoma volume.

Keywords: Low dose mifepristone, conservative management, leiomyomas, randomised controlled trial

Introduction
Leiomyoma is the most common benign tumour of uterus occurring in up to 20% of women with maximum incidence between 35-45 years of age leading to menorrhagia, pain and lump in abdomen. Incidence increases with age during the reproductive years such that cases occur in 20% to 50% of women older than 30 years. By extrapolation of findings from a prospective histopathology study of 100 consecutive total hysterectomy specimens, the prevalence of uterine fibroids in the general female population may be as high as 80% and is unchanged by menopausal status.
Fibroids are firm, compact tumours that are made of smooth muscle cells and fibrous connective tissue. Uterine fibroids are often described based upon their location within the uterus. Severity of symptoms typically depends on size, number of myomas, and tumour location. They represent one of the most frequent indications of operative procedures in woman of reproductive age group.
The self-reported prevalence of uterine fibroids ranged from 4.5% (UK) to 9.8% (Italy), reaching 9.4% (UK) to 17.8% (Italy) in the age group of 40-49 years.
Women with a diagnosis of uterine fibroids reported significantly more often about bleeding symptoms than women without a diagnosis heavy bleeding (59.8% vs. 37.4%), prolonged bleedings (37.3% vs. 15.6%), bleeding between periods (33.3% vs. 13.5%), frequent periods (28.4% vs. 15.2%), irregular and predictable periods (36.3% vs. 23.9%).

Furthermore women with diagnosed uterine fibroids reported significantly more often about the following pain symptoms: pressure on the bladder (32.6% vs. 15.0%), chronic pelvic pain (14.5% vs. 2.9%), painful sexual intercourse (23.5% vs. 9.1%) and pain occurring mid-cycle, after and during menstrual bleeding (31.3%, 16.7%, 59.7%, vs. 17.1%, 6.4%, 52.0%). 53.7% of women reported that their symptoms had a negative impact on their life in the last 12 months, influencing their sexual life (42.9%), performance at work & family (27.2%).

Aim of the study

3. To find the effectiveness of Mifepristone in the medical management of uterine leiomyomas.
4. To compare the dose response effect in the form of assessing the change in symptomatic profile and regression in volume of the fibroids. The present study compares the effect of 25 mg and 50 mg Mifepristone (administered once weekly for 6 months).

Definition

Uterine fibroids (myomas or leiomyomas) are benign, monoclonal tumours of the smooth muscle cells found in the human uterus. They arise from myometrial transformation as a result of specific physiological and pathological conditions. The majority of these monoclonal oestrogen-dependent uterine neoformations afflict mostly women during reproductive age, and 80% of them suffer from this during their whole lifetime. In the past, most women with fibroids remained undiagnosed, because they were asymptomatic. Analyses based on clinical diagnosis or diagnostic tests underestimate the true incidence; in fact, they take only into account symptomatic patients.

Incidence

As per a study done by Obstetrics and Gynaecology clinic in the year 2000, Worldwide about 20-40% women will be diagnosed with fibroid and the incidence is twice more common in black women than white. Prevalence Rate for Uterine fibroid is approximately 1 in 20 or 5.00% or 13.6 million people globally. It appears that African American women are much more likely to develop uterine fibroids. If a prevalence of 50% by 50 years of age is accepted, a large number of women have asymptomatic fibroids. As per a study conducted by the National Institute of Health in India about 25% of women in their reproductive years have noticeable fibroids. There are probably many more women who have tiny fibroids that are undetected. Fibroids develop in women between the ages of 30–50years. As per the Country/Region Extrapolated Prevalence population estimated to have uterine fibroid in India is 53,253,530 in a total population of 1, 065,070,6072. And also, it was observed that in 1000 of the fibroid uterus progresses into malignant lesions in the later stage.

A study was conducted in Karnataka during the year 2004-2007. The study concluded the incidence to be 2.97 percent. Factors that affected the prevalence of uterine fibroids included age at first birth, years since last birth, and younger age at menarche. Women who were parous had an incidence risk ratio of 0.7 relative to nulliparous women. Women who had a child of age less than 5 years of age were less likely to have uterine fibroids than those who had had a child 5 to 9 years previously. Finally, women who were older at menarche were less likely to have uterine fibroids than women who experienced onset of menses at 12 to 13 years. The current use of progestin-only injectables as birth control was associated with a 40 percent reduction in risk. Studies reported high levels of satisfaction on the part of the women assessed, measured at various points in time and along varied scales. They reported a range from 87 percent to 97 percent satisfaction with outcomes.

Type of study

- A prospective randomized control study

Period of study

- JANUARY 2016 –JUNE 2016

Place of study

- Gynaecology OPD &Gynaecology ward
- Department of Obstetrics &Gynaecology
- Govt Kilpauk Medical College &Hospital,

Inclusion criteria

1. Women of the age group 20-50 years.
2. Single or multiple leiomyomas, measuring > 5cm but less than 10cm.
3. Symptomatic myomas (symptoms like menorrhagia, dysmenorrhea, abdominal lump, dull aching lower abdominal pain, dyspareunia).
4. Parous women having living children
5. Nulligravidae with myomas resulting in infertility, not willing for surgical management.

Exclusion criteria

1. Adenomyosis
2. Endometriosis
3. Adnexal masses with the above symptoms
4. Liver or renal dysfunction
5. Current genital infection
6. Endometrial hyperplasia with atypia
7. Hormonal medication within 3 months
8. Women desiring pregnancy or are pregnant
9. Fibroids > 10 cm size and > 20 weeks size P/A.
10. Thyroid function disorders
11. Breastfeeding
12. Pelvic Inflammatory Disease
13. Malignancy

Sample size

The sample calculation was based on the study" Low dose Mifepristone for uterine leiomyomas by Vidushi Kulkshestha *et al*."

Relying on the previous experience and expecting a minimum difference of 13.2 % in the volume reduction of leiomyomas between study and control groups, the calculated sample size comes around 50 in each group with 90% power. The expected mean difference in volume reduction of fibroids is between 32.74-37.66 % from the original, with 7% margin of error.

Sample size -100, group i- 50, group ii-50

Materials and Methods

The present study was carried out as a prospective randomized controlled trial comparing the dose response effects of 25 mg and 50 mg weekly administrations of Mifepristone for 6 months. 100 patients satisfying the inclusion criteria were selected for the study. Mifepristone is available as 200 mg tablet (25 mg= $1/8^{th}$ of the tablet & 50 mg = $1/4^{th}$ of the tablet).

Patients were randomly allotted in 2 groups with 50 nos. in each group.

GROUP I was subjected to 25 mg of Mifepristone weekly for 6 months

GROUP II was subjected to 50 mg of Mifepristone weekly for 6 months

An informed consent was obtained from all the participants enrolled in the study. After enrollment, relevant medical history was taken and thorough physical examination was done. All the patients were subjected to pelvic USG examination to know the exact number, size, volume and location of myomas 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 myomas. As most of myomas are cuboidal, volume is calculated using formula 0.523×A x B x C. In case of multiple myomas, largest one (dominant) was used for volume calculation and follow-up. Blood samples were collected for haemoglobin, blood counts, baseline liver and renal function tests, bleeding time, clotting time, and an Endometrial Biopsy was done before starting and after the termination of treatment. Sonography was performed at the end of 24 weeks. Regression of clinical signs and symptoms / complaints and haematological assessment was done at final follow up at the end of 24th week. The outcome measures analysed were the change in volume and number of myomas and the diminution of symptoms. The results of these 50 patients were collected, tabulated and analysed.

Benefits of the study

1. This study evaluates the significant role of Mifepristone in the medical management of leiomyomas.
2. It compares the dose-response effect between 25mg and 50 mg of Mifepristone.
3. For decreasing intra operative blood loss while operating large sized myomas via Mifepristone's effect in reducing their blood supply.

Results

Table 1: From the above table the age distribution of Group MIF 25 and Group MIF 50 briefed.

Age Groups	Group MIF 25	%	Group MIF 50	%
≤ 30 years	8	16.00	3	6.00
31-35 years	13	26.00	4	8.00
36-40 years	10	20.00	17	34.00
41-45 years	11	22.00	21	42.00
46-50 years	8	16.00	5	10.00
Total	50	100.00	50	100.00

Table 2: Age distribution

Age Distribution	Group MIF 25	Group MIF 50
Mean	38.04	40.28
SD	6.57	4.82
*P value Unpaired t Test		0.0549

Results

Age groups table depicts the classification of subjects by age. It is evident from the result that 26.00% subjects were in the age group of 31-35 followed by 22.00% subjects in 41-45 years age group in MIF 25 group. Similarly, in MIF 50 group 42.00% subjects were in the age group of 41-45 followed by 34.00% subjects in 36-40 years age group. (p=0.0549, unpaired t test)

Discussion

During the process of statistically analysing age distribution between the intervention groups, the difference in the mean age of patients in MIF 25 group (38.04) and MIF 50 group (40.28) was found to be statistically insignificant (p >0.05).

Table 3: PBAC score (0 months) distribution

PBAC Score (0 months) Distribution	Group MIF 25	Group MIF 50
Median	103.50	100.00
Minimum	60	50
Maximum	140	126
P value Mann Whitney U Test		0.0802

Results

PBAC Score (0 months) groups table depicts the classification of subjects by PBAC score at 0 months. It is evident from the result that 46.00% subjects were in the ≤ 100 score group followed by 27.00% subjects in > 100 score group in MIF 25 group. Similarly, in MIF 50 group 52.00% subjects were in the ≤ 100 score group followed by 48.00% subjects in > 100 score group subjects, (p=0.0802, Mann Whitney U test)

Discussion

During the process of statistically analysing PBAC Score (0 months) distribution between the intervention groups, the difference in the median PBAC Score (0 months) of patients in MIF 25 group (103.50) and MIF 50 group (100.00) was found to be statistically insignificant (p >0.05).

Table 4: PBAC score (6 Months) distribution

PBAC Score (6 Months) Distribution	Group MIF 25	Group MIF 50
Median	32.50	20.00
Minimum	0	0
Maximum	65	45
P value Mann Whitney U Test		0.0174

Results

PBAC Score (6 months) groups table depicts the classification of subjects by PBAC score at 6 months. It is evident from the result that 100.00% subjects were in the ≤ 100 score group followed by none in > 100 score group in MIF 25 group. Similarly, in MIF 50 group 100.00% subjects were in the ≤ 100 score group followed by none in > 100 score group subjects, (p=0.0174, mannwhitney U test).

Discussion

During the process of statistically analyzing PBAC Score (6 months) distribution between the intervention groups, the difference in the median PBAC Score (6 months) of patients in MIF 25 group (32.50) and MIF 50 group (20.00) was found to be statistically insignificant (p<0.05).

The decreased difference in median PBAC Score (6 months) in MIF 50 group compared to MIF 25 group (17.50 points, 36% lower) was found to be statistically significant (p<0.05).

Further, Cohen's effect size value (d = 1.25) suggested a very high practical significance (90% study subjects in MIF 50 treatment group will have reduction in menstrual blood loss as outcome and 82% probability of superiority in outcome reduction compared to MIF 25 treatment group).

Table 5: Visual analog score (0 months) Distribution

Visual Analog Score (0 months) Distribution	Group MIF 25	Group MIF 50
Median	4.00	3.00
Minimum	1	1
Maximum	8	8
P value Mann Whitney U Test		0.0286

Results

VAS Score (0 months) groups table depicts the classification of subjects by VAS score at 0 months. It is evident from the result that 36.00% subjects were in the 3-4 score group followed by 30.00% subjects in 5-6 score group in MIF 25 group. Similarly, in MIF 50 group 40.00% subjects were in the 3-4 score group followed by 28.00% subjects in ≤ 2score group subjects, (p=0.0286, Mann Whitney U test)

Discussion

During the process of statistically analysing VAS Score (0 months) distribution between the intervention groups, the difference in the median VAS Score (0 months) of patients in MIF 25 group (4.00) and MIF 50 group (3.00) was found to be statistically significant (p<0.05).

The decreased difference in median VAS Score (6 months) in MIF 50 group compared to MIF 25 group (1.00 points, 25% lower) was found to be statistically significant (p<0.05).

Further, Cohen's effect size value (d = 0.54) suggested a high practical significance (71% study subjects in MIF 50 treatment group will have reduction in pain as outcome and 66% probability of superiority in outcome reduction compared to MIF 25 treatment group).

Table 6: Visual Analog Score (6 months) distribution

Visual Analog Score (6 months) Distribution	Group MIF 25	Group MIF 50
Median	1.00	1.00
Minimum	0	0
Maximum	4	3
P value Mann Whitney U Test		0.0445

Results

VAS Score (6 months) groups table depicts the classification of subjects by VAS score at 6 months. It is evident from the result that 80.00% subjects were in ≤ 2 score group followed by 20.00% subjects in 3-4 score group in MIF 25 group. Similarly, in MIF 50 group 92.00% subjects were in the ≤ 2 score group followed by 8.00% subjects in 3-4 score group subjects, (p=0.0445, Mann Whitney U test).

Discussion

During the process of statistically analysing VAS Score (6 months) distribution between the intervention groups, the difference in the median VAS Score (6 months) of patients in MIF 25 group (1.00) and MIF 50 group (1.00) was found to be statistically insignificant (p<0.05).

The decreased difference in median VAS Score (6 months) in MIF 50 group compared to MIF 25 group (0.44 points, 31.00% lower) was found to be statistically significant (p<0.05).

Further, Cohen's effect size value (d = 0.39) suggested a modeate practical significance (65% study subjects in MIF 50 treatment group will have reduction in pain as outcome and 61% probability of superiority in outcome reduction compared to MIF 25 treatment group).

Table 7: Myoma volume (0 months) distribution

Myoma Volume (0 months) Distribution	Group MIF 25	Group MIF 50
Mean	125.34	153.20
SD	49.55	48.42
P value Unpaired t Test		0.0054

Results

Myoma volume (0 months) groups table depicts the classification of subjects by myoma volume at 0 months. It is evident from the result that 38.00% subjects were in the ≤ 100

cm3 group followed by 32.00% subjects in 101-150 cm3 group in MIF 25 group. Similarly in MIF 50 group 36.00% subjects were in the 151-200 cm3 group followed by 30.00% subjects in 101-150 cm3 score group subjects, (p=0.0054, unpaired t test)

Discussion

During the process of statistically analysing myoma volume (0 months) distribution between the intervention groups, the difference in the mean myoma volume (0 months) of patients in MIF 25 group (125.34) and MIF 50 group (153.20) was found to be statistically significant ($p<0.05$).

The decreased difference in mean myoma volume (6 months) in MIF 50 group compared to MIF 25 group (27.86, 18% lower) was found to be statistically significant ($p<0.05$).

Further, Cohen's effect size value (d = 2.79) suggested a high practical significance (99% study subjects in MIF 50 treatment group will have reduction in myoma volume as outcome and 97% probability of superiority in outcome reduction compared to MIF 25 treatment group).

Table 8: Myoma volume (6 months) distribution

Myoma Volume (6 months) Distribution	Group MIF 25	Group MIF 50
Mean	77.46	42.50
SD	27.83	16.93
P value Unpaired t test		<0.0001

Results

Myoma volume (6 months) groups table depicts the classification of subjects by myoma volume at 6 months. It is evident from the result that 86.00% subjects were in the ≤ 100 cm3 group followed by 14.00% subjects in 101-150 cm3 group in MIF 25 group. Similarly, in MIF 50 group 100.00% subjects were in the ≤ 100 cm3 group (p= <0.0001, unpaired t test)

Discussion

During the process of statistically analyzing myoma volume (6 months) distribution between the intervention groups, the difference in the mean myoma volume (6 months) of patients in MIF 25 group (77.46) and MIF 50 group (42.50) was found to be statistically significant ($p<0.05$).

The decreased difference in mean myoma volume (6 months) in MIF 50 group compared to MIF 25 group (34.96, 45% lower) was found to be statistically significant ($p<0.05$).

Further, Cohen's effect size value (d = 3.50) suggested a high practical significance (100% study subjects in MIF 50 treatment group will have reduction in myoma volume as outcome and 98% probability of superiority in outcome reduction compared to MIF 25 treatment group).

Conclusion

We can conclude that:

- Age and PBAC Score (0 months) had no statistically significant role to play on influence on change in symptomatic profile and regression in volume of the fibroids
- When symptomatic profile and regression in volume of the fibroids were matched, the following conclusions was observed in MIF 50 treatment compared to MIF 25 treatment
- Better reduction in menstrual blood loss
- Higher reduction in pain
- Enhanced reduction in myoma volume

This study is a hypothesis proving study. Hence results have high clinical significance.

References

1. Sankaran S, Manyonda IT. Medical management of fibroids. Best Pract Res Clin Obstet Gynaecol. 2008; 22:655–76. [PubMed] [Google Scholar]
2. 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. [PMC free article] [PubMed] [Google Scholar]
3. 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. [PubMed] [Google Scholar]
4. Bagaria M, Suneja A, Vaid NB, Guleria K, Mishra K. Low-dose mifepristone in treatment of uterine leiomyoma: A randomised double-blind placebo-controlled clinical trial. Aust N Z J Obstet Gynaecol. 2009; 49:77-83.
5. Steinauer J, Pritts EA, Jackson R, Jacoby AF. Systematic review of mifepristone for the treatment of uterine leiomyomata. Obstet Gynecol. 2004; 103:1331-6.
6. 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.
7. Kapur A, Angomchanu R, Dey M. Efficacy of use of long-term, low-dose mifepristone for the treatment of fibroids. J Obstet Gynaecol India. 2016; 66:49-48.