

Safety And Efficacy Of Mifepristone In Different Dose (10 Mg And 25 Mg) For The Treatment Of Uterine Fibroids And To Evaluate Quality Of Life - A Randomized Double Blind Clinical Study

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Abstract

BACKGROUND: Mifepristone is Selective Progesterone Receptor Modulators (SPRMS) and is emerging as a best medical treatment increasing the quality of life as well as saving the patient from surgery. This drug has shown great effectiveness, e.g.: 2.5 mg, 5 mg and 10 mg, but with less reduction in uterine volume as well as reduction in fibroids size.

AIM: The aim of this study was to evaluate the safety and improvement of life pattern using 10 mg and 25 mg daily doses of Mifepristone for six months with a nine month follow-up period for the regress of fibroids as well as uterine volume to improve quality of life without any surgery in premenopausal women with complaint of menorrhagia, dysmenorrhoea, abdominal discomfort, dyspareunia, rectal pain, urinary problem and weakness due to anaemia.

METHODOLOGY: The research was a randomized double blind clinical study undertaken at MGM Medical College, Jamshedpur, (Jharkhand). The trial was done on 100 patients. Patients were divided into two equal groups (All were with symptomatic uterine fibroids) to evaluate safety as well as quality of life. Dose decided was 10 mg (A) and 25 mg (B) of Mifepristone. Subjects were taken from Gynaecological outdoor of MGM Medical College, Jamshedpur, (Jharkhand), after taking their consent. All women were between the age group of 35 to 48 years with symptomatic multiple fibroids of various sizes and site. At enrolment patients of both groups underwent clinical assessment, Per Abdomen (P/A) and Per Vaginal (P/V) examination, USG for uterine volume and size of fibroid. Endometrial biopsy was also done to note the changes prior to starting Mifepristone. Both groups A and B were advised to come at one month interval for clinical assessment and USG examination was performed to see the size of fibroids and uterine volume. At three months interval endometrial thickness associated with Mifepristone, Liver function test to see the level of Aspartate Transaminase (ASAT), Alanine Transaminase (ALAT) level and also other side effects of Mifepristone if any. Haematological examination was also performed at 1st visit and at 3 and 6 months' interval. This research is to give quality of life without side effects in a short period, eg: 3 to 6 months or even earlier.

RESULTS: Benign changes associated with PRM (Selective Progesterone Receptor Modulator) was diagnosed in (15/20) 75% and (12/20) 60% of patient in 25 mg and 10 mg group respectively. Elevation of hepatic transaminase were observed in only four cases. Complete amenorrhoea observed in 25 mg group and scanty and infrequent period in 10 mg group. Occasional hot flushes observed in 4 cases on 10 mg and 5 cases on 25 mg group. Relief in pressure symptoms was 98% in 25 mg group as compared to 72% in 10 mg group.

CONCLUSION: For better results, 25 mg Mifepristone can be given safely after proper scrutiny for earlier improvement.

Keywords: Mifepristone, Group A (10 mg) and Group B (25 mg), Fibroids.

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I. Introduction

A double-blind randomized clinical trial with two treatment groups to evaluate safety as well as improvement in quality of life using 10 mg and 25 mg dosing of Mifepristone daily over 6 months and follow-up was done for 9 months.

SUBJECTS

The patients were taken from Gynaecological outdoor of MGM Medical College Hospital, Jamshedpur, after taking their consent to participate in the study for 9 months in the year 2014-16. All were with symptomatic

uterine fibroids, ready to go for ultrasound examination of each evaluation, Endometrial Biopsies when needed as well as ready for Haematological examination and liver function test.

All subjects were between the age of 35 years to 48 years with symptomatic multiple fibroids of various sizes at different site. Both groups were advised to come at one-month interval for clinical assessment, USG examination to assess the size of fibroids, Uterine volume and Endometrial thickness. Blood samples were taken for Haematological as well as for LFT to see the level of ASAT and ALAT after 3, 6 and 9 months interval. Endometrial hyperplasia occurring after taking regular doses of Mifepristone is known as Progesterone Associated Endometrial Changes (PAECS).

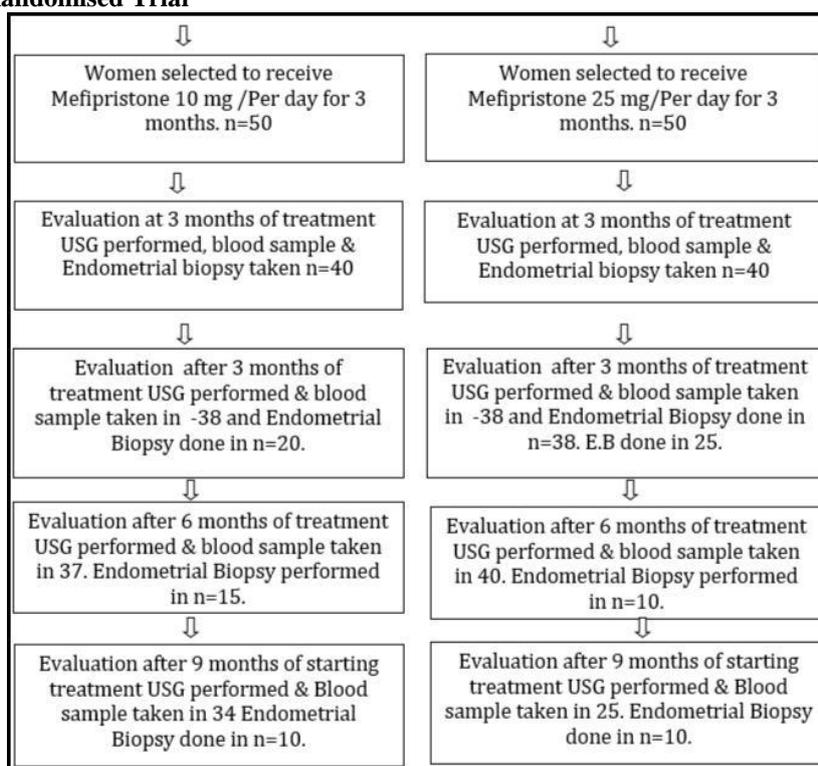
AIM

This research is to give quality of life without side effects in a short period, eg: 3 to 6 months or even earlier.

II. Material And Methods

In Gynaecological OPD of MGM Medical College, Jamshedpur, woman identified with symptomatic Leiomyomas = N-100. The number of woman accepted for the enrolment in the study, in them endometrial Biopsy and Ultrasound of Fibromyoma and Uterus performed and Blood sample taken n-100.

Flow Chart of Randomised Trial



Age of patient, History of patient onset of problem, Menstrual history, amount, duration, associated with pain or not, cycle regular or irregular noted. Pressure symptoms, Rectal pain, Urinary problem, Dyspareunia, H/o infertility and abortion noted. H/o of hepatic disease also taken.

After General, Abdominal and Gynaecological examination, the subjects were divided into two groups - One group (A) treated with 10 mg and other group (B) treated with 25 mg of Mifepristone. In all patients before starting treatment ultrasound of fibromyoma and uterus performed and blood sample taken. After starting treatment both groups were called at 3 months and 6 months interval for evaluation of treatment. For this USG performed, Blood sample taken and endometrial biopsy done. Same procedure repeated at 9 months as a followup.

Patients were given Mifepristone, which was supplied by Akumentis as a name of FIBROEASE of 10 mg and 25 mg.

Side effects of Mifepristone like amenorrhoea, hot flushes, nausea, sickness, vomiting, fatigue, tiredness were assessed. Any changes in hepatic transaminase prior to treatment and after 3 months and 6 months interval evaluated. During treatment period for evaluating safety, USG at 3 and 6 months interval done to note endometrial changes. Duration of irregular bleeding also estimated.

To evaluate effectiveness were the percentage changes in fibroids and volume of uterus before starting treatment and at and 6 months interval noted. Pre-treatment Biopsy performed in 40/100 cases. Proliferative changes was diagnosed in 12/40=30%. Secretory changes was diagnosed in 25/40=62.5% and unsuitable diagnosis was in 2/20=10%.

After three months of treatment, endometrial biopsy was done in 20/50 patients on 10 mg (A) Mifepristone and 25/50 patient on 25 mg, (B) Mifepristone. Benign changes (PAEC) associated with the use of PRM was diagnosed in 12/20, that is 60% in 10 mg (A). PRM was diagnosed in 15/20 (75%) patients on 25 mg (B). After 6 months 15/37 on 10 mg (A) benign changes in 60%, in 15/40 on 25 mg (B) benign changes noted in 62%.

On follow-up after 9 months, EB done in 10/50 on 10 mg (A) 20% and EB done in 10/50 on 25 mg (B) 20%. PAECs were diagnosed in 60% on 10 mg (A) and 64% in 25 mg (B) group. Two samples were unsuitable. In all cases PAECs, the average endometrial thickness was more than 15.0±3.5 mm and 12.0 ±3.5 mm in 25 mg (B) and 10 mg (A) Mifepristone group respectively.

According to various experts, the Histological changes occurring due to use of low-dose Mifepristone are not simple hyperplasia, but are presently known as Progesterone Associated Endometrial Changes (PAECs).^{2,3}

PAECs presents as a cyst-like dilation in the endometrial glands with occasional interior secretion, abnormal vessels and changes in the glandular connective tissue relationship. Percentage changes in the prevalence of symptoms - Menstrual disorder, Menorrhagia, Metrorrhagia, Dysmenorrhoea, Urinary symptoms, Pelvic pain, Rectal pain, Dyspareunia were evaluated at each visit. Transaminase only 3/80 (3.7%) with elevated transaminase at the end of 6 months treatments.

III. Results

Changes in fibroids volume in both groups after 3 months and 6 months treatment.

Fibroid Volume (CC)	Group A (10 mg)	Group B (25 mg)
Before		
	112±120	138±120
Treatment		
After 3 months	29% Reduction	39% Reduction
After 6 months	25% Reduction	30% Reduction

Both doses obtain results in reducing fibroids size. It was more with 25 mg dose. It remains constant lasting one year in high percentage of cases. In 10% of cases, small multiple fibroids had disappeared after 3 months of treatment.

Changes in uterine dimension before and after treatment - The average uterine volume was 20% and 53.9% of its pre-treatment size in 25 mg and 10 mg Mifepristone group. Endometrial thickness were 7.8±2.3 and 7±1.4 mm with 25 mg (B) and 10 mg (A) Mifepristone respectively.

Amount and type of Bleeding - Amenorrhoea was reported with 25 mg (B) group and very scanty period with 10 mg (A) group respectively at the end of 3 months and 6 months. It was a great relief to the patient of premenopausal age suffering from hypermenorrhoea.

List of prevalence of fibroids symptoms before and after 3 and 6 months treatment with 10 mg (A) and 25 mg (B) Mifepristone.

	Group A (10 mg) n 50	Group B (25 mg) n 50
Pelvic Pain		
Before Treatment	40	40
After 3 months treatment	7	3
After 6 months treatment	6	1
Pelvic Pressure		

Before Treatment	25	25
After 3 months treatment	2	1
After 6 months treatment	2	1
Urinary Symptoms		
Before Treatment	20	20
After 3 months treatment	2	1
After 6 months treatment	2	1
Rectal Pain		
Before Treatment	10	10
After 3 months treatment	2	1
After 6 months treatment	2	1
Dyspareunia		
Before Treatment	30	30
After 3 months treatment	5	5
After 6 months treatment	2	1
Hypermenorrhoea		
Before Treatment	40	40
After 3 months treatment	1	0
After 6 months treatment	3	0
Metrorrhagia		
Before Treatment	5	5
After 3 months treatment	0	0
After 6 months treatment	1	0

Evaluation of Quality of life was evaluated by means of UFSQOL (SPIES) test using the scale of 1 to 100 points to indicate quality of life. Quality of life significantly improved after improvement in pressure symptoms as well as menstrual symptoms, eg-Amenorrhoea, Hypomenorrhoea and disappearances of Dyspareunia and Rectal pain.

Improvement in Quality of life grouped in different section, eg: Sexual life, self-control, energy and mood was much better than 10 mg score and even more better than 25 mg as obtained by other authors. Ref.5 J.B. Spies, K. Coyne, et al. The improvement in Quality of life with 25% with 10 mg (A) group and 30% with 25 mg (B)

respectively. It was almost similar to the other methods of treatment, eg: Uterine artery embolization and even better than Myomectomy.

Effectiveness

Up to 6 months uterine volume decreases. Size of larger fibroids diminished significantly and small fibroids disappeared completely. (USG findings) with 10 mg (A) and 25 mg (B) fibroids volume reduces 25% and 30% respectively. There was significant improvement in menstrual pattern and remain same with 9 months treatment. Ref.4 Eisinger SH et al, Ref.5 Spies JB et al, Ref.8 Esteve JL et al.

UFS-QOL test score before and at the end of treatment with 10 mg and 25 mg Mifepristone using a scale of 1 to 100 patients.

	No. of Patients	10 mg (A)	25 mg (B)
Symptoms			
Before	50	40	45
After	50	15	05
Concern			
Before	50	60	65
After	50	75	80
Energy			
Before	50	70	70
After	50	76	85
Activity			
Before	50	70	70
After	50	80	80
Self-Control			
Before	50	70	70
After	50	75	80
Inhibition			
Before	50	65	70
After	50	75	80
Sexuality			
Before	50	70	70
After	50	76	80

Total 50+50

IV. Discussion

100 patients selected for study from the Gynaecological outdoor of MGM Medical College, Jamshedpur, with fibroids symptoms. They were divided into two equal groups to evaluate the safety as well as Quality of life after treatment with 10 mg (A) and 25 mg (B) of Mifepristone. Prevalence of fibroid symptoms before and after 3 and 6 months noted in both A and B groups and follow-up was done for 9 months.1,2,3,4

It has been noticed that reduction in fibroid volume after 3 months 29% in group A (10 mg) and 39% in group B (25 mg). After 6 months of treatment, there was 25% reduction in Group A as compared to 30% reduction in group B. In 10% of cases, small multiple fibroids had disappeared after three months of treatment.5,6,7,8

The average uterine volume was 20% and 53.9% of its pre-treatment size in 25 mg (B) and 10 mg (A). Significant reduction in uterine volume noted with 25 mg group (B) as compared to 5 mg and 10 mg group respectively.6,9

Endometrial thickness were 7.8±2.3 and 7±1.4 mm with 25 mg (B) and 10 mg (A) respectively. Amenorrhoea was reported with 25 mg (B) and very scanty period with 10 mg (A) respectively.7

Pelvic pain which was present in 80% of the patients before treatment remained 14% and 12% after 3 and 6 months treatment in group A (10 mg) and 6% and 2% with group B (25 mg). Pelvic pressure which was 50% before treatment remained 4% after 3 and 6 months treatment in group A (10 mg) and 2% only after 3 and 6 months treatment in group B (25 mg). Urinary symptoms which was 40% before treatment remained 4% in group A (10 mg) after 3 and 6 months treatment and only 2% with group B (25 mg) at same interval. Rectal pain which was present in 20% remain 4% and 2% with group A (10 mg) and group B (25 mg) after 3 and 6 months of treatment. Dyspareunia which was present in 60% of patient was reduced to 10% and 4% after 3 and 6 months of treatment in group A and 10% and 2% with group B. Hypermenorrhoea which was in 80% of

cases. After 3 and 6 months of treatment cured in 98% and 94%, after 3 and 6 months of treatment in group A (10 mg) and 100% in group B (25 mg).

Quality of life significantly improved after reduction in pressure symptoms and improvement in menstrual problem eg- Hypermenorrhoea, Dysmenorrhoea, Metrorrhagia as well as disappearance of Dyspareunia and Rectal pain.^{5,10}

Sexual life, self-control, energy and improvement in mood much better with 25 mg (B) than 10 mg (A) and even more better than 5 mg as obtained by J.B.

Endometrial biopsy was done in 20/50 patient on 10 mg (A) and 20/50 patient on 25 mg (B) Mifepristone. Benign changes (PAEC) associated with the use of PRN diagnosed in 12/20 patient (60%) in 10 mg group and 15/25 (75%) patient on 25 mg (B). After 6 months of treatment, benign changes noted in 60% in group A and 62% in group B. On followup after 9 months PAEC was diagnosed in 60% group A and 64% in group B. In all cases, average endometrial thickness was more than 15.0±3.5 mm and 12.0±3.5 mm in (B) and 10 mg (A) respectively. These changes due to use of Mifepristone are not simple, Hyperplasia but known as Progesterone Endometrial Changes (PAECs). J. Fiscella et al obtained almost similar proportion in 2.5 mg and 5 mg doses.⁷

Transaminase (ASAT and ALAT) were raised in 3.7% and 7% with 10 mg (A) and 25 mg (B) at the end of 6 months. The raised level was not very significant as compared to other.

As far as side effects of Mifepristone is concerned - Hot flushes were reported sometimes only in 8% and 10% in 10 mg and 25 mg groups. Vomiting reported only in 1% and 2% with 10 mg and 25 mg Mifepristone. Fatigue was noticed in 2% and 3% with 10 mg (A) and 25 mg (B) respectively.

V. Conclusion

Thus, it has been found that disappearance of symptoms was earlier with 25 mg (B) Mifepristone and also in those patient who had multiple and small size fibroids as compared to 10 mg (A) Mifepristone. This was a great relief for the patient as well as treating doctor. In my study, therefore, 25 mg Mifepristone is much better for earlier improvement in the patient as well as it is safe and also without significant side effects with improvement of quality of life. The acceptance was 99% and 6 months treatment is ideal.

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