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Original Research Article

Efficacy of different doses of mifepristone in the management of uterine leiomyoma in a tertiary care centre

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ABSTRACT

Background: Leiomyoma or uterine fibroid are benign tumours that arise from the smooth muscles of the uterus. The leiomyomas are common gynaecological problem encountered among reproductive age group women. Mifepristone is the commonly used drug in the management of uterine leiomyoma. The objective of the study were to study the efficacy and safety of 10mg and 25mg of Mifepristone in the management of uterine fibroid.

Materials and Methods: This is a randomized controlled Trial conducted in tertiary care centre. Hundred women with the diagnosis of uterine fibroid were taken up for the study. Group-A (n=50) were given Mifepristone 10mg and Group-B (n=50) were given Mifepristone 25mg daily for a period of 3 months. Reduction in the size of fibroid were assessed at the end of 3 months.

Results: At the end of 3months there was a significant reduction in both menstrual blood loss and fibroid volume in both the groups ($p<0.001$). There was a also significant improvement in haemoglobin levels in both the groups. When compared to Group –A (10mg Mifepristone) more side effects were noted in Group-B (25mg Mifepristone). Nausea and vomiting developed in 90% and 60% of patients in group A and B.Gastrointestinal discomfort developed in 80% and 50% of patients in group A and B.

Conclusion: Both Mifepristone 10mg and 25mg had similar clinical outcomes but 10mg had better compliance and lower side effects. Hence, 10mg can be preferred over 25mg in order to bring about effective management of uterine fibroid.

1. Introduction

Leiomyoma or uterine fibroids are benign tumors that arises from the smooth muscles of uterus.[1] Incidence is common in all age groups but more common among reproductive and perimenopausal age groups.[1] Based on the locaton, fibroids are classified into four types, submucousal, intramural, subserosal and transmural.[2] Out of these Intramural variety is found more commonly. Risk factors includes age, genetics, parity, increased body mass index and use of depot injections.[3–5]

Most of the patients are asymptomatic, those are the cases that are diagnosed incidentally during ultrasound examination which is done for other causes. If symptomatic, patients usually report with the complaints of heavy menstrual bleeding, lower abdominal pain, anaemia secondary to bleeding, back ache, dysmenorrhoea, dysparunia, non cyclic pelvic pain, pressure symptoms like constipation, infertility, recurrent miscarriage.[6] On examination patient presented with pallor, distended uterus with palpable knob like irregularities.[6]

Diagnosis is made by ultrasonography,[7] which is considered as basic and gold standard tool for the confirmation of diagnosis. Other options includes trans-

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vaginal ultrasound, saline infusion sonography, MRI and hysteroscopy.[7,8] Treatment opton includes both medical and surgical. Even though surgery is the end relief, medical or conservative management is more preferred by reproductive age group. In medical management various hormonal preparations are used to control heavy menstrual bleeding like.... and to reduce the size of the fibroid like.[9–11] Of those Mifepristone is the preferred drug of choice in the management of uterine leiomyoma.[12]

Mifepristone is a synthetic steroid that exhibits powerful antiglucocorticoid and antiprogesterone activity.[13] It directly acts on the fibroid causing reduction in the volume of fibroid.[13] Side effects of Mifepristone includes hotflushes, headache, gastrointestinal discomfort, nausea and vomiting, adrenal failure with higher doses.[14] The aim of the study were to study the efficacy and safety of 10mg and 25mg of Mifepristone in the management of uterine fibroid.

2. Materials and Methods

This is a randomized controlled trial conducted in shri sathya sai medical college at Kancheepuram district after obtaining Institutional ethical committee approval. One hundred women aged between 18 to 50 years with the diagnosis of uterine fibroid after confirmation with ultrasound were taken up for the study.

2.1. Inclusion criteria

1. Patient with the age of 18 to 50years.
2. Diagnosed fibroid cases of size >2.5cm -<7cm.

2.2. Exclusion criteria

1. Pregnancy.
2. Any other associated metabolic, hepatic, or renal complications.s
3. Patients who will directly undergo surgery for diagnosed fibroid uterus

Informed & written consent was obtained from the patient. A detailed history was taken and thorough clinical examination was done and all routine investigations were done. One hundred woman were randomly assigned by picking slots, where even numbers were receiving mifepristone 10mg and odd numbers were receiving mifepristone 25mg daily for 3 months (50 in each group). Abdominal ultrasonagraphy was performed before treatment and at end of 3 months to evaluate leiomyoma and uterine volumes. Efficacy was estimated by the reduction percentages of the leiomyoma and uterine volumes and the amount of menstrual blood loss.

Data was entered into Microsoft excel data sheet (MS-Excel) and analysed using the commercially available SPSS software package (statistical package for the social sciences) version 22. The association between categorical explanatory variables was assessed by the Chi-square test. The Independent t test was performed between continuous variable and categorical variable. P Value (probability that the result is true)- <0.05 considered as an association between variables.

3. Results and Observations

We found that among the study participants the mean difference of age, BMI, Blood pressure and parity usage between the groups was not statistically significant (p value >0.05).

Table 1: Comparison of mean of age between groups (N=100)

Parameter	Group (Mean± SD)		P value
	10 mg (N=50)	25 mg (N=50)	
Age	33.52 ± 8.04	33.82 ± 10.22	0.871
BMI	24.78 ± 2.53	25.62 ± 3.36	0.161
SBP	119.2 ± 6.43	120.48 ± 6.5	0.324
DBP	78.68 ± 5.29	76.76 ± 4.93	0.064

Among the study population, the mean difference of age, BMI, SBP, DBP between group was not statistically significant (p value >0.05).(Table 1)

Table 2: Comparison of parity between groups (N=100)

Parity	Group		Chi square	P value
	10 Mg (N=50)	25 Mg (N=50)		
Nulligravida	6(12%)	8(16%)	1.831	0.608
P1L0	4(8%)	2(4%)		
P1L1	16(32%)	12(24%)		
P2L2	24(48%)	28(56%)		

Among the study population, the difference in proportion of Parity between group was not statistically significant. (p value >0.05).(Table 2)

Comparison of parameters between pre and post treatment in Group-A and Group-B.

Among the study population, the difference in proportion of Menorrhagia, Metrorrhagia, Pelvic pain, status between group was statistically significant. (p value <0.05) (Table 3)

Among the study population, the difference in proportion of Urinary symptoms, Pelvic pressure, Dyspareunia, lumbar pain, Rectal pain between group was not statistically significant. (p value >0.05)

Among the study population, the difference in proportion of Urinary symptoms, Pelvic pressure, Dyspareunia, lumbar pain, Rectal pain between group was not statistically significant. (p value >0.05)(Table 4)

Among the study population, the difference in proportion of Menorrhagia, Metrorrhagia, Pelvic pain, status between group was statistically significant. (p value <0.05)

Among the study population, the difference in mean endometrial thickness, Fibroid dimension, Hb between

Table 3: Comparison of parameters between pre and post treatment (10mg) (N=50)

	Group			
Menorrhagia	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**P value**
Present	45 (90%)	4 (8%)	67.267	<0.001
Absent	5 (10%)	46 (92%)		
	Group			
Metrorrhagia	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**P value**
Present	10 (20%)	3 (6%)	4.332	0.037
Absent	40 (80%)	47 (94%)		
	Group			
Pelvin Pain	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**Fisher exact P value**
Present	7 (14%)	1 (2%)	4.891	0.059
Absent	43 (86%)	49 (98%)		
	Group			
Urinary symptoms	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**Fisher exact P value**
Present	7 (14%)	2 (4%)	3.053	0.160
Absent	43 (86%)	48 (96%)		
	Group			
Pelvic pressure	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**Fisher exact P value**
Present	6 (12%)	0 (0%)	3.945	0.060
Absent	44 (88%)	50 (100%)		
	Group			
Dyspareunia	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**Fisher exactP value**
Present	2 (4%)	0 (0%)	0.364	0.617
Absent	48 (96%)	50 (100%)		
	Group			
Lumbar pain	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**Fisher exact P value**
Present	3 (6%)	0 (0%)	1.083	0.362
Absent	47 (94%)	50 (100%)		
	Group			
Rectal pain	**Pre (N=50)**	**Post (N=50)**	**Chi square**	**Fisher exact P value**
Present	5 (10%)	0 (0%)	2.920	0.112
Absent	45 (90%)	50 (100%)		

group was statistically significant. (p value <0.05)(Table 5)

Among the study population, the difference in mean endometrial thickness, Fibroid dimension, Hb between group was statistically significant. (p value <0.05)(Table 6)

Among the study population, the difference in proportion of Nausea and Vomiting, Gastrointestinal discomfort between two groups was statistically significant. (p value <0.05) (Table 7)

Among the study population, the difference in proportion of Hot flushes, Headache between two groups was not statistically significant. (p value >0.05)

4. Discussion

Uterine fibroids are benign monoclonal neoplasms of the myometrium that represent the most common gynaecologic tumour.[1]

The medication most frequently used in the treatment of leiomyoma is mifepristone. Numerous investigations on the use of different mifepristone doses in the treatment of leiomyoma have shown that the greater the dose, the better the outcomes, including a reduction in the size of the myoma and a decrease in menstrual cycle blood loss, which raises haemoglobin levels. The primary negative effects at higher doses include endometrial hyperplasia and an increase in serum transaminases. The purpose of this study is to determine whether 10 mg has a similar efficacy to 25 mg while having a higher safety margin. As a result, the patient can be treated with greater patient satisfaction.

Our study was randomized controlled trial conducted at Department of OBG in Shrisathyasai medical college and research institute, Nellikuppam, Kancheepuram. We found that the mean age of our study participants among 10mg and 25 mg group was 33.52 ± 8.04 and 33.82 ± 10.22years respectively. This was corroborated by the study conducted by Geethamala et al. where they had found that Leiomyomas usually affected women between the ages of 31 and 40.[15]

We observed that most of the patients were ranging between 24 to 27 kg/m^2 of body mass index. The same was observed in a study conducted by Lee et al where they had observed that the mean BMI of the patients with leiomyoma was 22 kg/m^2. They also noticed that the weight gain in adult age is linked with increased risk of uterine

Table 4: Comparison of parameters between pre and post treatment (25mg) (N=50)

Menorrhagia	**Group**		**Chi square**	**P value**
	Before treatment	**After treatment**		
Absent	4 (8%)	48 (96%)	77.564	<0.001
Present	46 (92%)	2 (4%)		
Metrorrhagia	**Group**		**Chi square**	**P value**
	Before treatment	**After treatment**		
Absent	40 (80%)	49 (98%)	8.274	0.004
Present	10 (20%)	1 (2%)		
Pelvic pain	**Group**		**Chi square**	**P value**
	Before treatment	**After treatment**		
Absent	42 (84%)	48 (96%)	4.000	0.046
Present	8 (16%)	2 (4%)		
Urinary symptoms	**Group**		**Chi square**	**Fisher exact P value**
	Before treatment	**After treatment**		
Absent	44 (88%)	48 (96%)	2.174	0.269
Present	6 (12%)	2 (4%)		
Pelvic pressure	**Group**		**Chi square**	**Fisher exact P value**
	Before treatment	**After treatment**		
Absent	46 (92%)	50 (100%)	1.957	0.205
Present	4 (8%)	0 (0%)		
Dyspareunia	**Group**		**Chi square**	**Fisher exact P value**
	Before treatment	**After treatment**		
Present	3 (6%)	0 (0%)	1.083	0.362
Absent	47 (94%)	50 (100%)		
Lumbar pain	**Group**		**Chi square**	**Fisher exact P value**
	Before treatment	**After treatment**		
Present	1 (2%)	0 (0%)	0.000	1.000
Absent	49 (98%)	50 (100%)		
Rectal pain	**Group**		**Chi square**	**Fisher exact P value**
	Before treatment	**After treatment**		
Present	4 (8%)	0 (0%)	1.957	0.205
Absent	46 (92%)	50 (100%)		

Table 5: Comparison of mean of endometrial thickness between study group (10 mg) (N=50)

Parameter	**Study group (Mean± SD)**		**P value**
	Pre (N=50)	**Post (N=50)**	
Endometrial thickness in cm	9.09 ± 1.59	6.8 ± 1.59	<0.001
Fibroid dimension in cm	4.8 ± 1.27	3.84 ± 1.02	<0.001
Hb in %	6.34 ± 1.09	11.1 ± 1.09	<0.001

Table 6: Comparison of mean of endometrial thickness between study group (25 mg) (N=50)

Parameter	**Study group (Mean± SD)**		**P value**
	Pre (N=50)	**Post (N=50)**	
Endometrial thickness in cm	9.28 ± 1.58	7.04 ± 1.54	<0.001
Fibroid dimension in cm	4.76 ± 1.48	3.81 ± 1.19	<0.001
Hb in %	7.23 ± 1.2	11.12 ± 1.2	0.048

Table 7: Comparison of adverse effect between group (N=100)

Nausea a nd Vomiting	**Group**		**Chi square**	**P value**
	10 mg (N=50)	**25 mg (N=50)**		
Absent	45 (90%)	30 (60%)	12	0.000532
Present	5 (10%)	20(40%)		
Gastrointestinal discomfort	**Group**		**Chi square**	**P value**
	10 mg (N=50)	**25 mg (N=50)**		
Absent	40 (80%)	25 (50%)	9.890	0.0016
Present	10(20%)	25 (50%)		
Hot flushes	**Group**		**Chi square**	**P value**
	10 mg (N=50)	**25 mg (N=50)**		
Absent	46 (92%)	42 (84%)	1.515	0.218
Present	4 (8%)	8 (16%)		
Head ache	**Group**		**Chi square**	**Fisher exact P value**
	10 mg (N=50)	**25 mg (N=50)**		
Absent	48 (96%)	45 (90%)	1.382	0.436
Present	2 (4%)	5 (10%)		

leiomyomas.[16]

Kulkarni et al found that the most common benign uterine tumour, leiomyoma, primarily affects women who are childbearing age in their third decade (55%).[17] We found that it was very common among married women in our study.

Among the study population, the difference in proportion of Parity between group was not statistically significant. (p value >0.05). However, we noted that there was an increased number of leiomyoma cases in multiparous women than nulliparous women. Ibrar et al found that in the perimenopausal years, fibroids were discovered to be more common in multiparous women than nulliparous patients, which is indicative of their slow growth pace.[18]

Most of the subjects had primary level schooling years and were middle socio-economic class. This was supported by the study conducted by Seema Dayal et al. where they had observed similar results with respect to the mean years of schooling among leiomyoma patients.[19] Menorrhagia was common among both the groups. Menorrhagia is frequently brought on by fibroids, which are difficult to treat with traditional medical procedures. Although the exact mechanism underlying their impact on monthly blood loss is unclear, it may involve problems in local venous drainage, uterine cavity enlargement, and prostaglandin production.[20]

We also noted that there was a statistically significant reduction in the symptom of Metrorrhagia. We have found that there was a greater reduction in bleeding with respect to 25 mg than with 10 mg. This was supported by the study conducted by Kulshrestha et al. where they had observed that Mifepristone (10 and 25 mg) reduced menstrual blood by more than 90% and provided symptomatic relief. With a 25 mg dose, there was a greater reduction in myoma size.[21]

Other fibroid-related symptoms such as pelvic pressure and pain were considerably reduced in both groups as compared to the baseline (P 0.001) in both groups. Fiscella et al conducted a study which support our study results. They found that pelvic pressure and pain were considerably reduced in both groups as compared to the baseline (P 0.001) in both groups (10mg and 25mg). However, they noted that it was relatively effective with 25mg.[22]

Esteve et al found that increase in dosage of the mifepristone would help us to gain outcomes such as increase in average hemoglobin, changes in fibroid and uterine volume, and symptomatic improvement.[23] We also observed similar results in our study, however we also noted that there was a high significance in the 10mg group with respect to increase in average hemoglobin, changes in fibroid and uterine volume, and symptomatic improvement. This denotes that there was a similarity that existed among both the groups. Similarly, Steinauer J et al conducted a review and found that in published studies, mifepristone reduced the size of leiomyomas and improved symptoms.[24]

We found that nausea, vomiting, gastro-intestinal discomfort, hot flushes and headache were the common adverse effects in both 10mg and 25mg group. However, we also noted that the side-effects occurred in relatively more patients in 25mg group than in 10mg group. Among the study population, the difference in proportion of nausea and vomiting, Gastrointestinal discomfort between the groups was statistically significant. (p value <0.05). This was corroborated by the study conducted by Eisigner et al[25] where they had found that patients who were administered mifepristone 10 mg had lesser adverse outcomes in their study.

5. Conclusion

We found that patients who took 10mg Mifepristone had better compliance and lower side effects following administration than that of the 25mg group, although both their clinical outcomes were similar. Increase in average hemoglobin, changes in fibroid and uterine volume, and

symptomatic improvement were noted in both the groups.

Mifepristone may be a good option, particularly for unmarried women who want to avoid surgery and perimenopausal women whose myomas would regress following menopause. However, it can be used as a preoperative adjunct, particularly in patients with preoperative severe anaemia, large fibroids, where surgery is technically challenging, or where leiomyoma are unresectable. Although its use as a primary medical therapy is constrained due to recurrence after stopping treatment.

6. Source of Funding

None.

7. Conflict of Interest

None.

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