IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 5 Ver. VIII (May. 2016), PP 69-73
www.iosrjournals.org

"A Prospective Study to Evaluate the Effect of Mifepristone on Reduction of Size of Uterine Fibroid"

Seema Saharan (Ms)[1],Santosh Khajotia (Ms)[2],Swati Falodia (Ms)[3],Suman Budania (Ms)[4], Parul Prakash (Ms)[5]

[1]*Department Of Obstetrics & Gynaecology S.P. Medical College Attached To P.B.M. Associated Group Of Hospital, Bikaner (Rajasthan), India.*
[2]*Dr. Santosh Khajotia MS, Professor & Unit Head, Department Of Obst. & Gynaec, S.P. Medical College, Bikaner.*
[3]*Dr. Swati Falodia, MS, (Associate Professor) Department Of Obst & Gynaec., S.P. Medical College, Bikaner.*
[4]*Dr. Parul Prakash MS, (Assistant Professor), Department Of Obst & Gynaec, S.P. Medical College, Bikaner.*

Abstract
***Objective** : To evaluate the efficacy of low dose mifepristone treatment for 3 months on fibroid size and related symptom.*
***Design:** Prospective interventional analytic study.*
***Patients:** Twenty five patients with symptomatic fibroid, aged 20-50 years.*
***Intervention :** Patients received 10mg mifepristone daily for 3 months*
***Method :** Twenty five case of symptomatic uterine fibroids, were included in the study. The baseline data regarding the fibroid volume, Hb value, PBAC (Pictorial Blood Assessment Chart) & VAS (Visual analogue Scheme) score were compound with those recorded at the end of 1st month & 3rd months of therapy.*
***Results:** Mifepristone treatment significantly reduced fibroid volume from 91.13cm3 at enrollment to 38.73cm3 after 3months of treatment. The mean PBAC score was reduced for 111.52 at enrollment to 2.36 at the end of 3rd month of therapy.*

At 3 months 22 of 25 case (88%) developed amenorrhoea. At the end of the therapy hemoglobin value was raised by 2.38 gm/dL from the baseline value of 8.70mg./dL. There were no major side effects during the course of the study and treatment was well tolerated.
Conclusion: Low dose mifepristone (10mg) reduces fibroid size and related symptoms with minimal side effects among women with symptomatic fibroids.
***Keywords :** Mifepristone, leiomyoma, Fibroid*

I. Introduction

Uterine leiomyoma are the commonest benign gynaecological tumours occurring in up to 25 percent of women in reproductive age and about 40 percent have symptoms severe enough to warrant therapy[1], with peak incidence of symptoms occurring in women in their 30s and 40s.

Fibroids are the most common growth of the female reproductive tract, 2-3 times more common in Afro-Carribbean women. The definitive treatment for symptomatic myomas has always been surgical and myomas accounts for 40 percent of all hysterectomies in premenopausal women[2].

Non surgical treatment options for symptomatic myomas have limitations. Danazol reduces uterine volume by 18-23 percent, but is associated with marked androgenic side effects. Gonadotropin releasing hormone agonist reduces leiomyoma size to about 50 percent in three months but is expensive, has to be given parenterally and is also associated with hypoestrogenism leading to hot flushes, vaginal dryness and bone loss[3]. Cessation of GnRH causes regrowth of myoma and recurrence of symptoms. Uterine Artery Embolization has been shown to reduce leiomyoma size by 35-69 percent, but there are potential risks of premature ovarian failure and uterine synechia.

Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to oestrogen receptors and up regulates androgen receptors[4].

It is a well studied antiprogestin, which has been in use for over two decades for various clinical indications[5,6]. The effect of mifepristone on follicular development, ovulation, endometrial development and function is dependent on dose and timing of exposure[7].

II. Material & Methods

This prospective hospital based study was conducted in the Department of Obstetrics and Gynecology, P.B.M. and Associated Group of Hospitals, attached to Sardar Patel Medical College, Bikaner during study period of one year from 2014 to 2015.

All symptomatic cases of fibroid between 20-50 years of age with uterine fibroid more than 5cm on USG were included in the study. Exclusion Criteria were uterus size more than 20 weeks, Fibroids more than 15cm by USG, Renal or Hepatic dysfunctions, Suspected adenomyosis, Current genital infection and Endometrial hyperplasia with atypia and use of hormonal medication (Progestogens / GnRH) within 3 months.

The study was approved by Institutional Research Board, S.P. Medical College, Bikaner. Twenty five eligible women meeting the inclusion criteria were recruited from August 2014 to September 2015 in the study. Informed written consent was taken from all the participants. These patients were followed up at one and three months while on therapy. The results were compared from their initial visit symptoms & investigations.

Demographic and baseline clinical profile including details of menstrual cycle, symptoms and their severity was noted. According to WHO criteria hemoglobin less than 12gm/dL was taken as anemia (mild: 11.9-10gm/dL, moderate 10-7gm/dL, severe <7gm/dL). Menstrual blood loss was assessed by pictorial blood loss assessment chart (PBAC) scores[74], which is a semi-quantitative assessment that takes into account the number of pads soaked, their degree of soakage, passage of clots and episodes of flooding. A score of 100 or more accounts to menorrhagia.

Visual analog scale (VAS) score was noted for pain, dysmenorrhoea, dyspareunia, pelvic pain and pressure symptoms, where patients were asked to describe their pain on a scale of 0 to 10, before and after the treatment, with "no pain" taken at zero and "worst possible pain" at 100.

A complete general and gynaecological examination was done. Blood testing was done for hemoglobin, liver and kidney function tests. Ultrasound was done to confirm the diagnosis of leiomyomas as well as to ascertain number, site, volume of myomas and to rule out any other pelvic pathology. Volume of each myoma was calculated and added in cases with multiple myomas. Fibroid volume was calculated by the ellipsoid method and the formula V=0.5233(D1xD2xD3) was used, where D1, D2 and D3 are the longitudinal, transverse and cross-sectional diameters (in cm) of the fibroid, respectively. In multiple myomas, volumes of all myomas were added. Endometrial aspiration was performed to rule out any abnormal histopathology at the time of recruitment.

In this study mifepristone was given as 10mg/day, starting initially from day 2nd -3rd of period. Treatment was given for 3 months and patients were followed up at 1 & 3 months while on therapy.

Since mifepristone is available in India for induction of medical abortion as 200mg tablet, capsules of 10mg was prepared from 200mg tablet in the Pharmacology department by crushing the tablets in powder form, and then filling the capsules according to the weight.

III. Results

A total of 25 patients were recruits and followed up at Gynaecology outpatient department & all of them completed three months treatment duration.

Majority of the cases were in age group of 30-40 years in the study. The mean age of the patients in the present study was 37.16 years.

Excessive vaginal bleeding was reported by 82% cases, followed by backache & pain abdomen by 72% & 52% cases, respectively. Among AUB, 48% cases presented with menorrhagia while 32% and 4% presented with polymenorrhagia & menometrorrhagia, respectively. In two cases, fibroid presented with hypomenorrhea and same number of cases reported no menstrual irregularities.

The mean (range) baseline fibroid volume was 91.13 (30.77-432.70) cm^3 at the time of recruitment. The mean (range) fibroid volume at the end of the 1st month was 66.48 (17.41 - 371.75) cm^3, while at the end of 3rd month was 38.73 (2.763-146.94) cm^3 ($p<0.006$). The maximum no. of cases was presented with the fibroid volume $\leq 50cm^3$. The fibroid volume range 201-250 & >250 cm^3 were reported by minimum number of cases i.e. 1 (4%) in each range.

In our study mean baseline PBAC (range) at the time of enrollment was 111.52 (29-170). The mean PBAC score at the end of 1st month and 3rd month was 3.04 (0-38) and 2.36 (0-28), respectively ($p<0.0001$). Eighteen cases (72%) presented with a PBAC score range of 101-150. Minimum PBAC score (<50) was presented by 3 cases (12%). Maximum PBAC score (>150) was also presented by 3 cases (12%). Twenty two cases (88%) became amenorrhoeic at the end of treatment.

The mean VAS score of the cases at the time of recruitment in the study was 6.24±0.93. It was reduced to 2.28±1.14 at 1st month & 1.28±0.74 at 3rd month of treatment ($p<0.0001$).

The mean Hemoglobin value of the cases at the time of recruitment in the study was 8.70±0.37 gm/dL. It was increased to 11.08±0.42gm/dL at the end of 3rd month of the therapy ($p<0.0001$).

Liver enzyme were not affected after 3 month of mifepristone therapy showing mifepristone does not have any adverse effect on liver function on short term use for fibroid treatment. No serious adverse effect of drug was noted, however hot flushes, fatigue & headache each of the side effect was reported by one case (4%) due to antagonistic effect of RU486.

IV. Discussion

Uterine fibroids are very common non-cancerous (benign) growths that develop in the muscular wall of the uterus. While fibroids do not always cause symptoms, their size and location can lead to problems for some women, including pain and heavy bleeding.

The initiation and growth of myomas likely involves a multistep cascade of separate tumour initiators and promotors. Although the initiators of the somatic mutations remain unclear, the mitogenic effect of progesterone may enhance the propagation of somatic mutations. Oestrogen and progesterone appear equally important as promotors of myoma growth.

While there are no agents that could be described as definitive stand-alone treatments for fibroid disease, there is a wide range of agents that are used in aspects of the management of this common tumour. Gonadotropin releasing hormone agonist, selective oestrogen receptor modulators (SERMs), antiprogestins (RU486 and asnoprisinil), aromatase inhibitors, carbegoline, danazol and gestrinone are potential agents that have been used to varying degrees. The increasing knowledge of the biology of uterine fibroids is stimulating the development of newer non-hormonal therapies.

In the present prospective study 10mg dose of mifepristone has been used, as per the result of previous studies, 10mg of mifepristone was as effective as high doses (25mg & 50mg) with fewer side effects. V. Kulshreshtha et al[8] 2013 studied that 10mg RU486 is as effective as 25mg RU486 for treatment of uterine fibroid.

In our study, the majority of cases were in age group of 30-40 years, which correlates well with the age group most commonly found having fibroids and the related problems. In our study the mean BMI of the patients was 26.64kg/m^2, which shows that fibroids are more common in overweight and obese patients. The higher mean BMI is reflecting the hyper estrogenic state of the participants. Due to the availability of the limited data about the safety & efficacy of this drug, regarding future pregnancy, we did not included nulliparous & infertile women in our study.

Excessive Vaginal bleeding was the main problem for the women, compelling them to visit the health care facilities, as it affected their day to day activities; health status & work efficiency. This symptom was reported by 82% cases, followed by backache & pain abdomen by 72% & 52% cases, respectively.

The fibroid volume was reduced by 27% and 58% at the end of the 1st month and 3rd month, respectively. Fibroid volume reduced significantly from baseline to the end of the treatment ($p<0.006$). Though 1 of 25 cases showed enlargement in the fibroid size during the therapy however, she got enough relief in symptoms (both bleeding & pain).

Both Oestrogen Receptor and Progesterone Receptor are more abundant in leiomyoma cells than in the adjacent myometrium, suggesting that myomas are sex-steroid dependent tumours. Oestradiol & progesterone seem to stimulate myoma cells growth either directly or through mediation of growth factors. Progesterone also promotes the myoma growth by inhibiting the apoptosis of leiomyoma cells. Direct effect in reducing number of progesterone receptors, might be a mechanism of reduction of size of fibroid by mifepristone.

The similar results were obtained by Shikha Seth et al[9]. She observed 53.62% reduction in volume of dominate fibroid. The percentage decrease in size of fibroid in the studies done by Murphy AA et al[10] (in 25mg mifepristone group), Joseph Lluis et al[11] and Eisinger et al[12] (in 10mg mifeprisotne group) was 56%, 57% & 49%, respectively, which are comparable to our study. Sinha M. et al[13] observed 80% reduction in fibroid volume which was higher than our study.

The amount of bleeding was recorded using PBAC scoring system during all 3 visits & comparison of results were made. The PBAC score was reduced by 97% & 98% at the end of 1st month and 3rd month, respectively. Reduction in PBAC score was significant from baseline to at end of the treatment ($p<0.0001$) & the effect started from the first follow-up. This is due to the suppressive effect of RU486 on endometrial and vasculature by acting on VEGF. Twenty two cases (88%) became amenorrhoeic at the end of treatment. The probable hypothesis for amenorrhoea is that mifepristone delays or inhibit ovulation.

In the study conducted by V. Kulshreshtha et al[8], PBAC score was reduced to 92.4% and 96.4% while, 95.7% and 90.4% of patients developed amenorrhoea in 10mg and 25mg mifepristone group, respectively. These results are comparable to our study.

The patients were followed for 3 month for the amount of the pain felt, on a pain analogue scale. There was 63% & 79% reduction in the pain score at the end of 1st month & 3rd month of therapy, respectively, in our study. Backache was reported by 72% of the patients at start, which reduced to 20% at the end of therapy (P value <0.043). There was a significant reduction in complain of backache at the end of the therapy. The

improvement in other pain related symptoms were not significant, however the severity of the pain symptoms were decreased significantly (P<0.001).

In our study hemoglobin value was raised by 8.6% & 27% at the end of 1st month and 3rd month of the treatment, respectively. The improvement in hemoglobin value was significant in our study (p value 0.0001). At the end of the therapy hemoglobin value was raised by 2.38 gm/dL from the baseline value of 8.70 gm/dL. Similar results were noticed by Shikha Seth et al[9], She observed that Hb values were raised by 2.8 gm/dL at the end of the therapy.

Although this study had few methodological problems i.e. no long term follow up period and small sample size. However, results have shown that mifepristone caused significant reduction in fibroid size and alleviated fibroid related symptoms. Further studies are needed to determine that how long the benefits of the drug will sustain after discontinuation of treatment and what would be the adverse effects of the drug if it is used for a prolonged period. The treatment was well tolerated by all the participants as evidenced by adherence of the patients to the treatment & minimal side effects.

Conclusion:

Low dose mifepristone showed a speedy & better control of bleeding and alleviation of pain related symptoms that improved the general condition of women, relieved their anxiety, provided them a sense of well being with a few side effects.

Mifepristone can be used for temporary relief of symptoms for short periods. This application is suitable in women with symptomatic fibroids in perimenopausal years or in patients not suitable for surgery due to medical reasons.

Bibliography

[1]. Adamson GD. Treatment of uterine fibroids current findings with gonadotropin releasing hormone agonists. Am J Obstet Gynecol 1992; 166 : 746-51.

[2]. Carlson KJ, Nichols DH, Schiff I. Indications of hysterectomy. N Engl J Med 1993; 328 : 856-60.

[3]. Lethaby A, Vollenhoven B, Sowter M. Preoperative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2001: CD000547.

[4]. Spitz IM. Clinical utility of progesterone receptor modulators and their effect on the endometrium. Curr Opin Obstet Gynecol 2009; 21 : 318-24.

[5]. Gemzell-Danielsson K, Marions L. Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception. Hum Reprod Update 2004; 10:341-48.

[6]. Gemzell-Danielsson K, Swahn ML, Svalander P, Bygdeman M. Early luteal phase treatment with mifepristone (RU 486) for fertility regulation. Hum Reprod 1993;8:870-73

[7]. Lalit Kumar PG, Lalitkumar S, Meng CX, Stavreus Evers A, Hambiliki F, Bentin Ley U, Gemzell Danielsson K. Mifeprostone. but not levonorgestrel. inhibits human blastocyst attachment to an in vitro endometerial three dimesional cell culture model. Hum Repord 2007:22:3031-37.

[8]. Vidushi Kulshrestha, Alka Kriplani, Nutan Agarwal, Neeta Sareen. Low dose mifepristone in medical management of uterine leiomyoma: An experience from tertiary care hospital from North India. Indian J Med Res 2013; 137: 1154-62.

[9]. Seth S, Singh E, Mathur AS, Gupta G. Low dose mifepristone (25mg) in treatment of uterine myoma, in perimenopausal women. J South Asian Feder Menopause Soc 2013; 1(1):34-37.

[10]. Murphy AA, Kettel LM, Morales AJ, Roberts VJ and Yes SS. Regression of uterine leiomyomata in response to the antiprogesterone RU 486. Fertri steril 1995; 64 (1): 187-90.

[11]. Josep Lluis Carbonell, Rita Acosta, Yasmirian Perez, Roberto Garces. Treatment of Uterine Myoma with 2.5 or 5 mg Mifepristone Daily during 3 Months with 9 Months Posttreatment Followup: Randomized Clinical Trail. ISRN Obstetric and Gynecology 2013; 10: 1155-63.

[12]. Eisinger SH, Meldrum S, Fiscella K, Le Roux HD and Guzick DS. Low-dose mifepristone for uterine leiomyomata. Obstet Gynecol 2003; 101: 243-250

[13]. Sinha M. Kayal A, Mukhopadhay P. Effecitveness of mifepristone in the treatment of uterine leiomyomata. N J obstet Gynecol 2013; 8(1):22-25.

Table -1: Baseline Characteristics of Participants

Demographic Data	Mean	SD
Age (in year)	27.16	5.54
BMI (Kg/m2)	26.64	1.99
Parity	2.88	1.48
Duration of Symptoms (in month)	12.28	9.52
PBAC Score	111.52	36.86
VAS Score	6.24	0.93
Fibroid volume (cm^3)	91.13	87.74
Hemoglobin (gm/dL)	8.70	0.37

Table 2: Distribution of cases according to resolution of the Pain Related Symptoms

Pain Related Symptoms	At Ist Visit		At 3rd Month		P value
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	
Backache	18	72	5	20	0.043
Dysmenorrhoea	7	28	2	8	0.239

Pain Lower Abdomen	13	52	5	20	0.177
Heaviness at Lower Abdomen	4	16	1	4	0.417
Dyspareunia	2	8	1	4	0.973

Table 3: Comparison of cases according to PBAC Score

PBAC Score	At Ist Visit		At Ist Month		At 3rd Month	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
≤ 50	3	12	25	100	25	100
51-100	1	4	0	0	0	0
101-150	18	72	0	0	0	0
151-200	3	12	0	0	0	0
TOTAL	25	100	25	100	25	100
Mean ±SD	111.52 ± 36.85		3.04 ± 8.55		2.36±6.89	

Table 4: Comparison of cases according to VAS Score

VAS Score	At 1st Visit		At 1st Month		At 3rd Month	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
No Pain (0)	0	0	1	4	3	12
Mild Pain (1-3)	0	0	20	80	22	88
Moderate Pain (4-6)	15	60	4	16	0	0
Severe Pain (7-10)	10	40	0	0	0	0
TOTAL	25	100	25	100	25	100
Mean ±SD	6.24 ±0.93		2.28 ± 1.14		1.28 ± 0.74	

Table 5: Comparison of cases according to Fibroid Volume

Fibroid Volume (in cm^3)	At 1st Visit		At 1st Month		At 3rd Month	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
≤50	10	40	13	52	19	76
51-100	9	36	9	36	5	20
101-150	2	8	2	8	1	4
151-200	2	8	0	0	0	0
201-250	1	4	0	0	0	0
>250	1	4	1	4	0	0
TOTAL	25	100	25	100	25	100
Mean ± SD	91.13 ± 87.74		66.48 ± 70.43		37.73 ± 30.55	

Table No. 6 Comparison of present study with main Clinical Studies on Mifepristone for Uterine Myomas

Studies	No. of Patients	Mifepristone dose (mg/day) Orally	Duration of treatment (moths)	Reduction in Fibroid Volume (%)
Present Study	25	10	3	58
Murphy et al 1995	9	5	3	26
Murphy et al 1995	11	25	3	56
Eisinger et al 2003	16	5	6	48
Eisinger et al 2003	16	10	6	49
Fiscella and colleagues 2006	22	5	6	40
Joseph Lluis et al 2008	50	5	3	57
Joseph Lluis et al 2008	50	10	3	45
M. Bagaria et al (2009)	20	10	3	30
M. Engman et al (2009)	15	50	3	34
C. Feng et al2010	43	5 or 2.5	6	18
Sucheta Mukharji et al2011	30	25	6	160 ml
V. Kulshreshta et al 2013	70	10	3	36
V. Kulshreshta et al 2013	73	25	3	22
Sinha M et al(2013)	50	25	3	80
Shikha Seth et al (2013)	93	25	3	46
Gil M. Yerushalmi et al 2013	33	10 (Vaginally)	3	25