To Compare the Efficacy of Ulipristal acetate and Mifepristone in Management of Uterine Fibroids in Symptomatic Patients of Reproductive Age Group

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ABSTRACT

Introduction: Uterine myomas incidence is variable as most of the patients are asymptomatic but most common clinical feature which makes women seek their treatment are menorrhagia and iron deficiency anaemia leading to chronic fatigue. Study aimed to compare the efficacy of UPA and mifepristone in medical management of uterine fibroids in symptomatic patients of reproductive age group.

Material and methods: A prospective randomized observational study was carried out, in women with single or multiple uterine leiomyoma. Exclusion criteria: severe anemia, using any hormonal therapy, with suspected carcinomas or with adnexal masses. 100 patients were randomly allocated to two subgroups; group A receiving 5 mg UPA and group B receiving 25 mg Mifepristone daily, for 13 weeks. PBAC was used to assess menstrual blood loss and Likert score for other symptoms. Baseline variables: uterine size and volume, Myoma size and volume, number, hemoglobin, liver function tests were noted and reassessed at 1, 3 and 6 months. Endometrial sampling was done initially and at the end to study.

Results: Mean fibroid volume reduction was 35.23% in group A and 33.45% after 13 weeks' treatment in group B. Mean reduction in menorrhagia: 84% in group A and 52.5% in group B. 91% cases experienced amenorrhoea in group A and 72% in group B.

Conclusion: UPA 5mg was better at achieving significant reduction in menorrhagia and achieving amenorrhoeic state as compared to Mifepristone.

Keywords: Medical Management Myomas, Ulipristal Acetate (UPA), Mifepristone.

INTRODUCTION

Uterine myomas are the commonest occurring benign hormone sensitive, smooth muscle tumors occurring in about 20-40% women of reproductive age group.[1,2] They are also the commonest indication for hysterectomy. Other symptoms include dysmenorrhoea, pelvic pain and pressure symptoms adversely affecting the quality of life. Besides patient's age the choice of treatment is guided by symptoms and desire for future fertility. Along with being a surgical trauma, hysterectomy also poses a great mental stress to the women.

Current studies support that growth of myoma in humans is progesterone dependent also and that estrogen is required only for up-regulation of progesterone receptors[3] therefore antiprogestins (Mifepristone) and selective progesterone receptor modulators (SPRMs-Ulipristal acetate) can be effective in treatment. Various medical therapies available in market as an alternative to surgical management have their limitations. GnRH agonists are approved only for short term therapy owing to safety concerns[4] and breakthrough bleeding associated with progestin limits their use.[5]

Mifepristone has strong affinity for endometrial progesterone receptors and up-regulates androgen receptors.[6] It targets and decreases the number of progesterone receptors in leiomyomas. Increase in androgen receptors contributes to mifepristone's anti-proliferative effects. Estrogen dependant endometrial proliferation and secretory function is suppressed. It also has direct vascular effect which alters the blood flow to the leiomyomata. All these effects along with inhibition or delay in ovulation result in amenorrhea.

Researchers have used mifepristone in doses ranging from 5mg to 50mg per day for periods ranging from 3 to 12 months with significant symptomatic improvement. Studies have shown that lower doses are equally effective in decreasing fibroid volume. An effective dose to cause a clinically significant (50%) decrease in fibroid volume appears to be 25mg daily.[7]

Ulipristal acetate, a selective progesterone receptor modulator (SPRM) acts on progesterone receptors in myometruim and endometrium, inhibiting ovulation without any significant effects on estradiol levels or anti-glucocorticoid activity.[8] Various researchers along with PEARL studies have already suggested benefits of SPRMs. A 3 month course of ulipristal acetate in dose from 5mg to 20mg per day significantly reduces fibroid volume and control heavy bleeding, although

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studies have confirmed no advantage of high dose over low dose.

These two drugs – Ulipristal acetate and Mifepristone provide effective medical alternative to surgical treatments available for symptomatic fibroids. This study was carried out to compare the efficacy of these two drugs in managing symptomatic uterine fibroids.

MATERIAL AND METHODS

This was a prospective randomised observational study carried out for a period of three years (2015-2018) at Kalpana Chawla Government Medical College, Karnal after approval by institutional ethical committee. Before enrolling in the study, patients were informed about the treatment and written informed consent was obtained from each patient. A total of 100 patients were randomly allocated into two groups of 50 each according to whether they received UPA (5mg OD): group-A or Mifepristone (25mg OD): group-B for a period of 13 weeks.

Women presenting with single or multiple symptomatic fibroid uterus, with a uterine volume of more than 200c.c. were selected for this study. All these women agreed to use of non-hormonal methods of contraception during the study period and were in good general health.

Patients with severe anaemia (Hb <7g%)/hepatic/renal/respiratory dysfunction or blood clotting disorders, those having concomitant adenomyosis or pregnancy, any suspected adnexal masses, suspected carcinoma cases were excluded from study. Women using hormonal contraception or HRT within three months or using GnRH analogues 6 months prior to study were also excluded.

A detailed history, demographic profile and thorough general physical examination was done for each patient. A thorough menstrual history was recorded to note the degree of menorrhagia, menometrorrhagia, polymenorrhoea and dysmenorrhoea. Other symptoms like bladder frequency, pelvic pain or pressure symptoms were also noted. Baseline evaluation included: a complete blood count, renal and hepatic function tests, ultrasonography for fibroid and uterine volumes/sizes and an endometrial sampling. Fibroid volume was calculated by formula: 4/3 lxbxh cm3 (where l,b,h are radii of fibroid in three dimensions). During measurement in cases with multiple fibroids, the largest fibroid was studied and cervical length was excluded in all cases as it varies in different people. Endometrial sampling was performed initially to rule out malignancy and later to visualize the histopathological changes with the drug.

Pictoral blood loss assessment charts (PBAC) were distributed to each patient and used to assess the blood loss. Likert score was used to assess other symptoms of -dysmenorrhoea, menorrhagia, pressure symptoms and dyspareunia. After baseline evaluation the women were followed up for a period of over six months and re-evaluated for the above variables at the end of first, third and sixth month. The primary outcome was evaluated in terms of change in fibroid volume and reduction in menstrual blood loss. Secondary end points include improvement in hemoglobin and symptomatology, changes in bleeding pattern and onset of amenorrhoea and any unbearable side effects.

RESULTS

Administration of drugs in both the groups was associated with reduced menstrual blood loss, dysmenorrhea and reduction in fibroid volume. Out of 100 studied cases the

Parameter	Study Category	Baseline	3rd month	6th month
Haemoglobin (g/dl)	A	8.1 g/dl ± 0. 32	11.8 g/dl ± 1.82	11.4 g/dl ± 0.42
	B	8.1 g/dl ± 0.51	11.3 g/dl ± 1.26	10.9 g/dl ± 0.45
PBAC Score	A	380	70	79
	B	248	18	35

Table-1: Showing baseline haemoglobin and PBAC scores and subsequent follow up.

Symptom	Study Category	Baseline	1 Month	3 Months	6 Months	P Value	Improvement
Menorrhagia	A	45	1	0	8	0.000	84%
	B	40	2	1	19	0.000	52.5%
Metrorrhagia	A	24	2	0	3	0.000	87.5%
	B	18	2	0	5	0.000	72.2%
Polymenorrhoea	A	30	1	0	2	0.000	93.3%
	B	28	0	0	6	0.000	78.5%
Dysmenorrhoea	A	28	1	1	1	0.000	96.42%
	B	32	1	2	9	0.000	71.87%
Bladder Frequency	A	35	30	12	11	0.000	68.5%
	B	31	24	8	20	0.000	35.4%
Pelvic Pain	A	38	15	10	13	0.000	65.78%
	B	38	18	7	24	0.000	36.8%
Pelvic Pressure	A	40	31	18	19	0.000	55%
	B	30	20	11	17	0.001	43.3%

Group A (UPA) n = 45, Group B (mifepristone) n = 40. * The differences were highly significant. ($p < 0.000$)

Table-2: Showing menstrual and pelvic symptomatology at the start of therapy and subsequent follow up.

Parameter	Baseline		1 Month		3 Months		6 Months	
	A	B	A	B	A	B	A	B
Mean uterine volume	320.25	256.82	275.42	231.14	214.19	174.64	217.26	188.74
% fall	-	-	14.01%	10%	33.12%	32%	32.16%	26.51%
Mean myoma volume	92.4	81.12	78.15	71.39	59.96	55.99	60.52	58.77
% fall	-	-	15.43%	12%	35.23%	33.45%	34.51%	27.56%

Table-3: Changes in volume of uterus and fibroid: baseline evaluation and follow up.

mean age was 37.47 years +/- 4.2 in group A and 36.38 years +/- 3.9 in group B. Mean parity in cases was 4 (range 2- 7). Mean BMI was 24.12 kg/m2 +/- 3.42 in group A and 25.28 kg/m2 +/- 2.49 in group B.

There was statistically and clinically significant reduction in fibroid volumes in both the groups (table 3). Menstrual bleeding was controlled significantly in about 90% women in group A and 75% women in group B (table 2). There was significant reduction in bleeding (Medium change in PBAC score > 300) in group A, whereas the reduction (Medium change in PBAC score of 230) was little less in comparison in group B (table 1). Excessive bleeding was rapidly controlled in both groups by end of first month of treatment. At the end of 3 months' therapy, amenorrhoea developed in 91% patient in group A and 72% in group B, but on re-evaluation at end of sixth month from start of therapy, it persisted in only 86% women in group A and 65% in group B. The hemoglobin levels were higher in group A after initiation of treatment (table1).

The reduction in myoma volume, was 15.43% at the end of 4 weeks' treatment in group A and 12% in group B. Although marked reduction was appreciable by end of three months' treatment in both groups (table 3).

The side effects were bearable in both the groups and did not lead to discontinuation of drug in either group. Headache (10%) was the commonest reported side effect in group A women and managed with counseling and simple analgesic. Others were hot flushes, breast pain and nausea. In group B women leg cramps (11%) and atypical hot flushes (6%) were the only reported side effects. All the endometrial samplings done showed benign histology without hyperplasia. Repeat endometrial histopathology did not reveal any complex hyperplasia or atypia in either group.

By the end of study period, two patients lost follow up in group A and one patient opted out for hysterectomy during first month of treatment. In group B, two patients lost follow-up, one opted out for hysterectomy by end of second month of treatment and one deviated from the protocol. During follow up at the end of sixth month from initiation of therapy, two patients required hysterectomy in group A and six patients underwent hysterectomy in group B.

DISCUSSION

Abnormal uterine bleeding is major cause of concern in women as it affects their work efficiency and health status, therefore mostly opt for hysterectomy as one-time management in developing countries.

Many clinical trials using 5-50 mg doses of Mifepristone have been conducted for varying periods (3 to 12 months) but exact dose and the duration for most effective therapy are yet to be determined. Murphy et al were first to describe use of mifepristone in treatment of uterine fibroids.[7] Study by Kettle et al., reported amenorrhoea in 40-70% cases over one year at 5-10 mg dose, while 100 mg led to 100% amenorrhoea.[9] Eisinger, et al, reported fall of 48% in mean uterine volume while amenorrhoea persisted in only 61% after 6 months of 10 mg mifepristone therapy.[10] The present study showed a decline in fibroid volume by 12%, 33.45% and 27.56% at the end of 1st month, 3rd month and 6th month of treatment with 25mg Mifepristone, while the amenorrhoea persisted in only 65% after 6 months therapy. This is comparable to study carried out by Nanda et al demonstrating a fall of 11.1%, 32.1% and 27.2% at the end of the 1st, 3rd and 6th month of treatment.[11] However it was lower than the reduction reported by Murphy et al (76.3%). There is a positive evidence that treatment with mifepristone relieve heavy menstrual bleed as compared with placebo.[12,13] There was a marked reduction in menstrual blood loss as depicted by a significant decline in PBAC score from 248 to 18 by 3rd month of drug usage.

Similarly, Ulipristal acetate has been tested in many RCTs. PEARL-1 study compared it with placebo and found significant improvement in menorrhagia in 91%, 92% and 19% of women receiving UPA 5mg OD, 10 mg OD and placebo respectively. These results were comparable to our study. The improvement in dysmenorrhoea and menstrual complaints was 96.4% and 91% respectively. Amenorrhoea was achieved in 91% patients in study which is slightly higher than (82%) achieved in study conducted by Donnez et al.[14]

Our study found that though improvement in symptomatology from baseline was significant with both the drugs, the effect was better in group A as compared to group B. Similar results were reported by study carried out by Kale AR in 2018.[15] The fall in myoma volume was higher in group A at the end of 3 months (35.23%) than group B (33.45%) and it significantly persisted in group A (34.51%) at the end of 6 months follow up than group B (27.56%), amenorrhoea developed in 91% patients in group A and 72% in group B, but at 6th month of follow up, it persisted only in 86% group A and 65 in group B.

Woman's compliance and acceptance of medical management protocol is clear from the low drop out in both the groups (A: 5/50 and B: 10/50) and up to 90% post-treatment follow-up rate. Acceptance is high because it is really cost effective (no hospital admission, preoperative tests, blood transfusion, surgical and medicinal charges).

CONCLUSION

Treatment of symptomatic fibroids with Ulipristal acetate

and mifepristone was associated with significant reduction in fibroid volume, blood loss and other associated symptoms. The fibroid volume reduction and amenorrhoea were persistent in group A on discontinuation of drug. We found that UPA was more effective in controlling menstrual and pelvic symptoms and in reducing myoma as well as uterine volume without significant side effect in comparison to mifepristone which is a cheaper option to women in our country.

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