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ORIGINAL ARTICLE

Lower Dose of Ulipristal Therapy: Comparison of 2.5 versus 5 mg for Efficacy and Safety in Medical Management of Uterine Fibroids

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ABSTRACT

Objective: To compare the efficacy of 2.5mg versus 5mg ulipristal acetate in reducing symptoms (menstrual blood loss and pelvic pain) and volume of uterine fibroids.

Design: Randomized controlled trial, conducted at All India Institute of Medical Sciences, New Delhi. Recruitment was terminated after 40 patients in June 2018, after MHRA advisory.

Methods: Women with symptomatic uterine fibroids, with PBAC score >100 with or without pelvic pain and at least one fibroid >3cm diameter, were recruited and randomized into two groups: group 1 (n=20) received 2.5mg ulipristal acetate and group 2 (n=20) received 5mg ulipristal acetate once daily for 13 weeks.
Assessment of PBAC scores and fibroid volume by ultrasound were done at baseline, after 3 months of therapy and then 3 months after discontinuation of therapy i.e. at 6 month follow-up. Liver functions were evaluated at 3 and 6 months follow-up.

Results: Significant reductions in PBAC scores occurred in both groups. Median (interquartile range) of PBAC scores reduced from 282 (124–1384) to 34 (0-385), in

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the 2.5mg group and 362 (128–940) to 0 (0- 284) in the 5mg group showing .87.5% and 100% reduction respectively. Further reduction after 3 months on treatment was as 0 ((0- 185) and 0 (0-322), p=0.001 in group1 and 2 respectively(p=0.001), 3 months after stopping treatment, score increased to 122(0-1312) & 165(0-560) however reduction from baseline in both groups 56.7 & 54.4% respectively. Amenorrhoea occurred in 6(30%) and 13(65%), 15(75%) & 16(80%) after1mth, 3mths on therapy and 4(20%) & 1(5%) 3months after treatment in 2.5 and 5mg group respectively. Normal periods achieved in 8(40%), 3(15%) at 1 month, 2(10%) & 1(5%) at 3mths and 4(20%) & 6(30%) cases in gp1 & 2 respectively.

VAS remained significantly reduced in both groups even after stopping drug Median fibroid volumes reduced significantly in the 2.5mg group [(79.63cm3 (27.35-148.04) to 51.3cm3 (2.52-82.86), 35.58%, p=0.002] but less in the 5mg group baseline 83.31cm3 (33.99- 309.8)] to 74.61cm3 (18.-283.64), 10.44%, p=0.526] Monitoring of liver functions showed increased SGOT and SGPT up to 222 and 399 in group 2 at 3 months follow-up which became normal in 3 months' time. Monitoring of liver functions tests in both groups did not reveal any abnormalities. Neither dose of ulipristal suppressed estradiol.

Conclusions: Treatment with 2.5mg Ulipristal acetate for 3 months is a feasible option in terms of symptoms control when compared to 5 mg dose. Rebound phenomenon is more with higher dose. With concerns of side effects with 5 mg dose, chief aauthor suggests to give 2.5 mg dose as it can be safer option. Further larger well powered studies may be conducted with lower doses of ulipristal for fibroid management.

KEYWORDS

• Fibroids • Myoma • Ulipristal Acetate • Medical Management

INTRODUCTION

Fibroids are benign tumors, affecting up to 40% of women.[1] Although a benign disease, fibroids are the reason for 40-60% of hysterectomies.[2] Until the advent of gonadotropin releasing hormone analogues (GnRH), medical therapy for fibroids aimed at symptomatic control. GnRH analogues reduced fibroid size also and paved a way for medical therapy which offered an alternative to surgical management. However, due to its considerable side effects, GnRH agonists cannot be offered for a period longer than 6 months. Research revealed that the progesterone is the true crucial factor in fibroid tumorigenesis, and that the primary roles of estrogen and its receptor are permissive ones, enabling the tissue to express progesterone receptors (PR). Hence selective progesterone receptor modulators (SPRMs) emerged as a preferred medical solution. Ulipristal acetate, a SPRM, reduces fibroid size by a combination of proliferation inhibition, transitory stimulation of apoptosis and extracellular matrix (ECM) remodeling by increasing expression of matrix metalloproteinase-2 (MMP-2). This reduction in ECM is responsible for a sustained fibroid shrinkage observed even after the treatment cessation.[3] Donne established the dose of once daily 5mg ulipristal acetate orally for 13 weeks, for medical therapy for fibroids after a series of randomized controlled trials and the drug was FDA approved for fibroids. The serious adverse effect of liver toxicity was observed in some patients leading to its ban in 2018. Later the ban was lifted with a rider for only short course of 3 months permissible for patients planned for surgery.

This study was planned before the ban to establish efficacy of lower ulipristal dose, which would significantly decrease the cost burden of this treatment, with a more favorable safety profile. This study compared 2.5mg vs. established 5mg dose.

MATERIALS AND METHOD

A randomized controlled trial was conducted at outpatient department of a tertiary referral center in New Delhi, India, between July 2016

and November 2018, after obtaining approval of the Ethics Committee of the institute. Inclusion criteria was women aged 18-50 years with heavy menstrual bleeding defined as a PBAC score >100, with or without the presence of pelvic pain or dysmenorrhea, and at least one fibroid >3.0 cm in one dimension. Exclusion criteria included post-menopausal status, FIGO types 0-1 fibroids, uterine size >20 weeks, history of receiving medical or hormonal treatment for fibroids in the last 3 months, suspected adenomyosis suspected clinically or on ultrasound, history of uterine artery embolization, suspected or known gynecological cancer or atypical endometrial hyperplasia.

This was planned as a pilot study with sample size of 60 subjects but with the temporary ban on prescribing ulipristal acetate as advocated by the RCOG[8], this trial was terminated after recruitment of 40 subjects with 20 subjects in each arm. All patients were recruited after taking written informed consent.

A detailed history was elicited for menstrual cycle characteristics and fibroid related symptoms – heavy menstrual bleeding (HMB), pelvic pain, and pressure symptoms. Menstrual blood loss was assessed using a Pictorial blood Loss Assessment Chart (PBAC) score. A PBAC score >100 was taken as HMB. Pelvic pain severity was assessed by Visual Analog Scale (VAS). Patient were asked to mark on the given pictorial VAS score on days of pelvic pain in her menstrual cycle. The average of VAS score was included in the study. General physical and systemic examination, per abdomen, per speculum and bimanual examinations were done. Baseline blood tests included hemoglobin, platelet count, bleeding and clotting times, blood glucose, liver function tests, kidney function tests and serum TSH. Ultrasound findings were noted.

Transabdominal ultrasound with 2-4MHz convex probe and/or transvaginal ultrasound using 5.0-7.5MHz endovaginal probe (Voluson E8 and Logic P6 machines) were used to document the uterine size; endometrial thickness; number of fibroids, fibroid size measured in three dimensions, location and FIGO type. Myoma volume was calculated according to probate ellipsoid formula (height x length x width x 0.5233) and expressed in cm3. In multiple fibroids, myoma volume was calculated as the sum total of the three largest uterine fibroids).

The subjects were then randomized using computer generated random numbers into two groups in blocks of 10. Group 1(n=20) received tablet ulipristal acetate 2.5mg orally once daily, and Group 2 (n=20) received tablet ulipristal acetate 5mg orally once daily for 13 weeks. Treatment was started within 5 days of menstrual cycle. Follow up were done thrice: at 4 wks. on treatment, after completing 3 months (13 weeks) treatment, and 3 months after cessation of treatment. PBAC and VAS scores were recorded at each visit. Ultrasound was repeated for myoma volume after 3 month therapy and 3 months after stopping it. Serum estradiol levels were estimated at the end of the treatment course.

Following the advisory warning by the Medicines and Healthcare products Regulatory Agency (MRHA) published in February 2018, all recruited patients were informed of the concerns of liver toxicity with ulipristal acetate. Patients were educated regarding red flag signs and symptoms of liver toxicity: nausea, vomiting, upper abdominal pain, decreased appetite, tiredness or yellowing of the eyes or skin, and were monitored with monthly liver function tests. Those patients who had completed treatment prior to the warning, were contacted and asked to undergo liver function tests at the third follow-up. Further recruitment was terminated in June 2018. Primary outcomes were menstrual blood loss and fibroid volume. Secondary outcomes were the effect on pelvic pain, serum estradiol levels and the persistence of these effects three months after cessation of therapy.

Statistical Analysis

Data analysis was carried out using statistical software STATA version 12.0. Comparison between the studies groups were tested with Students'-independent test. Variables from baseline to follow-up were compared using t-paired test. For non-parametric data, Mann-Whitney U-test and Wilcoxon Signed Rank test were used, as applicable. For all statistical tests, a two-sided probability level of $p<0.05$ was considered as statistical significance.

RESULTS

Total 40 women with symptomatic uterine fibroids were recruited. The baseline

demographic and clinical characteristics of the two groups were comparable and is outlined in table 1.

Table 1: Baseline demographic and clinical characteristics between two groups

Characteristics	Group 1 (n=20)	Group 2 (n=20)	p Value
Age (years) Mean ± S.D.	36.2±8.58	37.95±8.11	0.512
BMI (kg/m^2) Mean ± S.D.	25.81±4.58	24.94±5.90	0.601
Duration of Heavy menstrual bleeding (months) Mean ± S.D.	31.65±40.33	28.60±31.90	0.751
VAS scores Mean ± S.D.	4.75±2.51	4.45±2.44	0.704
PBAC score Median (range)	282(124-1384)	362 (128-940)	0.34
Haemoglobin (gm/dl) Mean ± S.D.	10.57±1.55	11.38±1.58	0.114
T. Bilirubin (mg/dl) Mean ± S.D.	0.44±0.23	0.50±0.18	0.328
SGOT (IU/L) Mean ± S.D.	27.2±9.76	27±13.42	0.957
SGPT (IU/L) Mean ± S.D.	29.4±20.65	22.55±12.09	0.208
ALP (IU/L) Mean ± S.D.	155.6±66.6	145±88.94	0.685
Estradiol (pg/ml) Median (IQR)	37.12(28.43-56.33)	69.5(53.44-95.0)	0.04
Fibroid Volumes (cm^3) Median (IQR)	79.63 (27.35-148.04)	83.31 (33.99-309.8)	0.752.
Endometrial thickness (mm) Median (IQR)	5.55 (4.0-10.18)	6.3(4.48-9.23)	0.946

Baseline serum estradiol levels varied significantly between both groups, which can be attributed to the wide range of estradiol levels in premenopausal female (15-350pg/ml). None of the participants in either groups had values in the postmenopausal ranges (<10pg/ml).

Effect on menstrual:

Effect on median PBAC score with therapy is shown in Fig 1 and table 2. Median PBAC score was 0 at 3 months in both the groups which increased 3 months after cessation of treatment, but was still lower than the baseline PBAC. Significant and comparable reductions in PBAC scores occurred in both the groups.

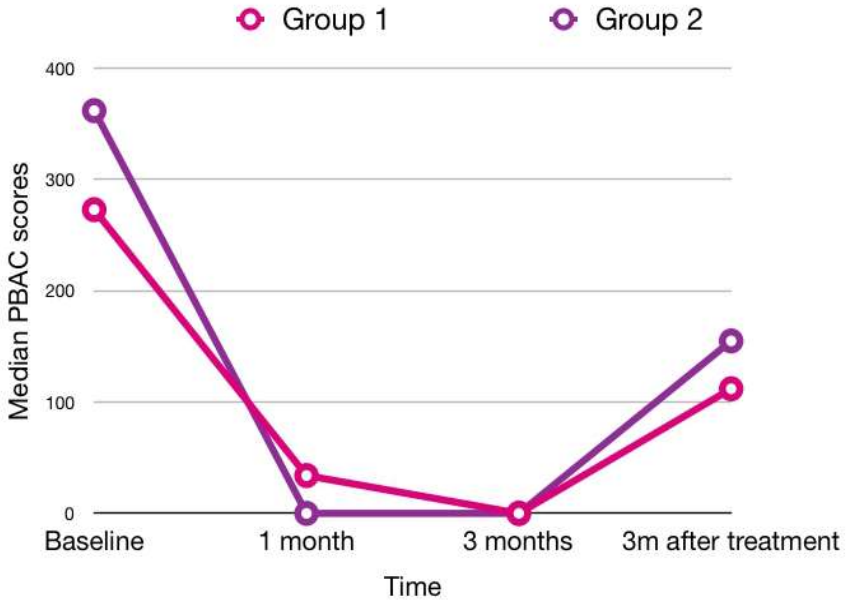

Figure 1: Comparison of median PBAC score over time among groups

Table 2: Effect of treatment on PBAC score in both group

	Group 1 (n=20)	Group 2 (n=20)
Baseline median (range)	282 (124-1384)	362 (128-940)
At 1 months		
Median (range)	24 (0-385)	0 (0-284)
% **reduction from baseline**	87.9%	100%
p value	p=0.001	p=0.001
At 3 months		
Mean ± SD (Median)	0(0-284)	0(0-322)
Change from baseline	96%	95%
p value	0.002	0.002
At 6 months (3mths post-treatment)		
Median (range)	122 (0-1342)*	165(0-560)
Change from baseline	56.7%	54.4%
p value	0.01	0.01

*Based on 19 patients (1 patient did not complete follow up} in group1)

Mean PBAC scores were also calculated which decreased from baseline 530 ± 425 to 225±217 cm3 and 376±199 to 72±128 cm3at 1st month, with further reduction to 20±47 and 31±99 cm3 at 3 months which increased 3 months after stopping therapy to 364±541 and 198±154 cm3 in group1 and group 2 respectively. There was reduction in tune of 76% and 81% at 1st month, 96% and 91% at 3 months in group1 and 2 respectively, (p=<0.001). PBAC score increased after stopping therapy yet was lesser than the baseline, showing reduction up to 31% and 47% in the respectively. Pattern of fall is similar as median levels.

Significantly more subjects were amenorrhoea in group-2 receiving 5mg after 1 month of therapy (p=0.027). However, amenorrhoea rates were comparable in both groups at the end of 3 months of therapy (p=0.342). Menstrual pattern with treatment is shown in table 3.

Table 3: Menstrual pattern at various followups in both groups

Menstrual patterm	Groups	baseline	1 month	3 months	6 months
Amenorrhoea	Gp 1	0 (0%)	6 (30%)	15 (75%)	4 (20%)
	Gp 2	0 (0%)	13 (65%)	16 (80%)	1 (5%)
Normal menstrual flow	Gp 1	0 (0%)	8 (40%)	2 (10%)	4 (20%)
	Gp 2	0 (0%)	3 (15%)	1 (5%)	6 (30%)
Heavy menstrual bleeding	Gp 1	20 (100%)	6 (30%)	2 (10%)	11 (55%)
	Gp 2	20 (100%)	4 (20%)	3 (15%)	13 (65%)

Effect on fibroid volume:

Effect of treatment on fibroid volume as measured by ultrasound at baseline, after 3 months of therapy and 3 months after cessation of therapy is shown in table 4.

Table 4: Effect of treatment on median myoma volume in group1 and group 2

Fibroid volume (cm3)	Group 1 (n=20)	Group 2 (n=20)
Baseline Median (IQR)	79.63 (27.35-148.04)	83.31 (33.99-309.8)
At 3 months		
Median (IQR)	51.3 (12.52-82.86)	74.61(18.04-283.64)
Change from baseline	35.58% reduction	10.44% reduction
p value	0.002	0.948
At 6 months (3mths post-treatment)		
Median (IQR)	50.82* (13.87-153.53)	87.16 (18.96-282.19)
Change from baseline	36.62% reduction	4.62% increase
p value	0.002	0.627

*based on 19 patients (1 patients did not complete follow up)

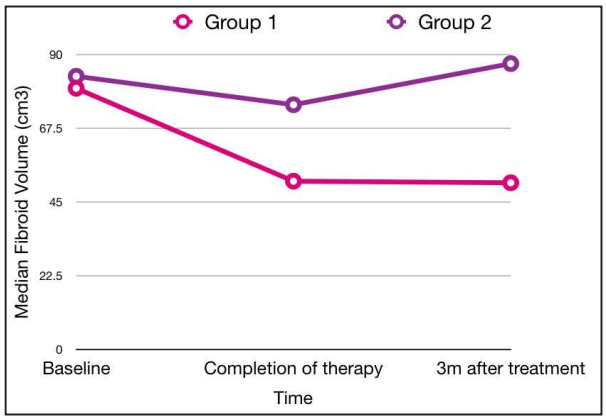

Figure 2: Comparison of median myoma volume over time among groups

A subgroup analysis was done for fibroid volumes less than 100 cm^3 and more than 100 cm^3 as shown in table 4 (fig 3) and table 5 (fig 4) respectively.

In the population with **fibroid volume <100 cm^3 at baseline**

Table 4: Effect of treatment on myoma volume in patients with baseline fibroid volume <100cm^3

Fibroid volume <100 cm^3	Group 1 (n=13)	Group 2 (n=11)
Baseline Median (IQR) (cm^3)	64.18(16.55 – 79.63)	38.39 (28.13- 60.01)
At 3 months		
Median (IQR) (cm3)	15.68 (8.93-51.30)	22.61(9.86-65.08)
Change from baseline	75.5%	41.1%
p value	0.006	0.248
At 6 months (3mths post-treatment)		
Median (IQR) (cm^3)	18.88*(12.40-76.49)	30.46(10.55-77.76)
Change from baseline	70.58%	20.66
p value	0.117	0.286

*Based on 18 patients (Ultrasound not done in 2 patients)

A significant reduction (75%) in myoma volume was seen with 2.5 mg ulipristal acetate but not with 5mg (41.1%). Neither group had statistically significant decreased myoma volume 3 months post-treatment.

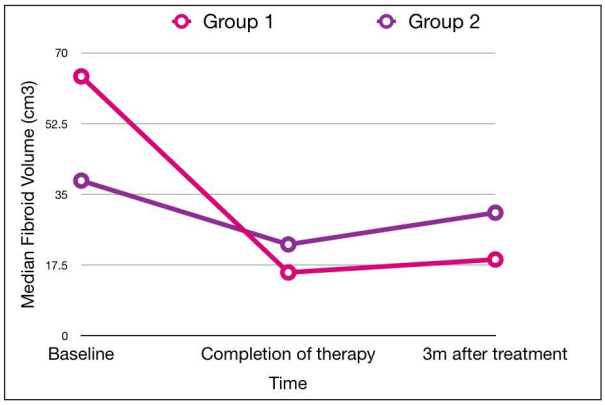

Figure 3: Comparison of median myoma volume among groups (baseline fibroid volume <100cm^3)

In the population with **fibroid volume >100 cm^3 at baseline**

Table 5: Effect of treatment on myoma volume in each group in patients with baseline fibroid volume >100cm^3

Fibroid volume >100 cm^3 (cm^3)	Group 1 (n=7)	Group 2 (n=9)
Baseline Median (IQR) (cm^3)	276.13 (142.98–378.65)	322.24 (129.97-339.25)
At 3 months		
Median (IQR) (cm^3)	121.45 (67.64-412.5)	306.48 (125.82-404.10)
Change from baseline	56.01% Reduction	4.89% Reduction
p value	0.128	0.859
At 6 months (3mths post-treatment)		
Median (IQR) (cm^3)	417.10 (66.56- 3337.91)	282.43 (136.11-425.63)
Change from baseline	51.05% Increase	12.35% Decrease
p value	0.173	0.859

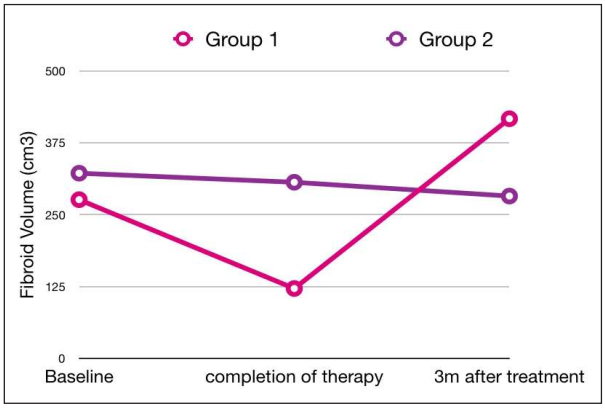

Figure 4: Comparison of median myoma volume over time among groups (baseline fibroid volume >100cm^3)

In Group 1, the median fibroid volume underwent a 55.99% reduction from baseline after completion of treatment course. Three months after discontinuation of therapy, median fibroid volume grew from 121.45cm3 (IQR: 67.64-412.5) to 417.10cm3 (IQR: 66.56-3337.91), however this change is not significant. These results of Group 1 were likely influenced by a patient with large baseline fibroid volume of 1450.48cm3, which reduced to 1106.49cm3 after treatment, but appeared degenerated. 3 months after completing therapy, patient complained of abdominal pain and increasing abdominal distention. On ultrasound, the fibroid had grown significantly (volume – 9817.48cm^3). She underwent a hysterectomy. Intraoperatively, the uterine size was 28 weeks with a 30x25x25cm fibroid with areas of cystic degeneration but grew to 9817.48cm^3. As shown in figure 4, the large fibroids in Group 2 responded minimally to treatment.

Total 13(65%) of subjects receiving 2.5mg and 40% receiving 5mg ulipristal acetate had >25% reduction in fibroid volume from the baseline and 30% of each group had >50% reduction after 3 months of treatment, which was comparable. More than 75% reduction

was observed in only 2(10%) and 1(5%) cases of group1 and 2 respectively (p=0.99) after stopping the therapy reduction was similar in both doses in 25% (50% &35%) p=0.3), 50% reduction in 27 and 25% {p=0.99) and <75% in 16% and 10%) p= 0.6)

Effect on pelvic pain:

Table 5: Effect of treatment on pelvic pain VAS score in each group

VAS Score:	Group 1 (n=20)	Group 2 (n=20)
Baseline Mean± S.D	4.75**±2.51**	4.45**±2.44**
At 1 months		
Mean **±SD**	1.35**±1.84**	1.00**±1.86**
% **reduction from baseline**	71.58%	77.53%;
p value	0.001	0.001
At 3 months		
Mean **±SD**	0.95**±1.82**	0.45**±1.40**
% **reduction from baseline**	80%	89.89%
p value	0.001	0.001
At 6 months (3mths post-treatment)	2.21±3.05*	3.05±2.87
Mean **±SD**		31.46%;
% **reduction from baseline**		0.036
p value		

*Based on 19 patients (1 patient did not complete follow up)

Subjects of both groups experienced significant and comparable reductions in pain scores, evident after 4 weeks of treatment as shown in table 5. Three months post-treatment, VAS remained significantly reduced in both groups compared to the baseline (53.47% reduction p=0.001 in Group 1; and 31.46% reduction, p=0.036, in Group 2).

Effect on serum estradiol:

Post-therapy, the median estradiol levels in Group 1 was 41.5pg/ml (IQR: 25.25-63.5) and 65pg/ml (IQR: 34.75-74.25) in Group 2 There was no significant change in estradiol levels after therapy in either group, and no patient had post-menopausal levels after therapy.

Adverse effects:

Fatigue and bloating was reported by one case in each group. Headache, weight gain and breast tenderness was observed in 1, 2 and 1 case with 5 mg dose. None of the patients in either group complained of hot flushes.

Liver toxicity:

None of the patients reported any features of liver toxicity – nausea, vomiting, upper belly pain, lack of appetite or yellowing of the eyes or skin. There were 13 patients who were receiving the drug after the warning released by the MHRA of UK. They underwent monthly liver function tests, which were within normal limits except 1 case in group-2 whose SGOT and SGPT were 222 and 399 after 3 months treatment and reverted back to normal range in 3 months post-treatment.

DISCONTINUATION RATES AND FAILURE OF THERAPY

In group-1, one patient underwent hysterectomy due to failure of therapy without completing treatment period; another 24-year-old unmarried girl had 71% increase in fibroid size and increased PBAC score after completing post-treatment follow up, she received GnRH treatment followed by myomectomy 6 months later. No reduction in PBAC score was seen in one more patient in group 1 and two cases in group 2. Two cases underwent hysterectomies after 6 months of follow-up. One patient with recurrent abortions underwent myomectomy after completion of follow up as a part of infertility treatment.

DISCUSSION

Fibroids are benign condition still they are the reason for 40-60% of hysterectomies (5). In the present study, treatment with both 2.5mg and 5mg ulipristal acetate resulted in a significant control of menstrual blood loss, reduction in size of fibroid and relief of pelvic pain. Both groups attained significant reductions if PBAC scores within 1 month of treatment (87.9% in group 1 and 100% in group 2) and at the end of 13 weeks (100% in both groups).

A significant reduction from the baseline persisted in the both groups, 54.4%; and 57.7% in patients receiving 5mg and 2.5 mg ulipristal acetate which was comparable, p=0.3.

The efficacy with 5mg Ulipristal observed in the present study is comparable to that reported in literature. In PEARL I study, Donne investigated the efficacy of a 3 month course of 5mg and 10mg ulipristal acetate and demonstrated that menstrual bleeding was controlled in 91% of the women receiving 5mg ulipristal acetate and in 92% of the women receiving 10mg ulipristal acetate, as compared to only 19% of the women who received placebo.

In PEARL II study, reduction in uterine

bleeding was seen in 90% women receiving 5mg of ulipristal acetate, 98% in the group receiving 10mg of ulipristal acetate, and 89% in the group receiving leuprolide acetate (6, 7) Our study observed that even further reduced dose of ulipristal to 2.5 mg/day was effective in symptomatic relief as well as reducing fibroid volume. When mifepristone was studied for medical management of fibroids, the minimum dose found effective was much lesser than the initially studied doses. In fact this was the basis for conceptualizing the present study with lower dose of ulipristal.

In a retrospective study by Brun *et al*[9], after 3 months of treatment with 5mg ulipristal acetate, a PBAC score of <75 was obtained in 43/55 (78%) of previously menorrhagia patients. The efficacy of 2.5mg ulipristal acetate was found comparable to the efficacy reported with 5mg dose published in other studies.

In our study, amenorrhoea occurred earlier with 5 mg dose, in 13(65%) cases just after 1 month of therapy, whereas it was seen in 6(30%) cases with 2.5 mg dose. However, at 3 months treatment similar rates of amenorrhoea was seen: 15(75%) and 16(80%) respectively in group 1 and group 2. This was similar to amenorrhea rates varying from 73-89% observed with 5mg and 10mg ulipristal in previously published studies (6,7,10). Our results indicate that reduction of ulipristal dose to 2.5mg does not drop the efficacy, rather the rebound phenomenon was noticed more in higher doses, 4 times more cases with smaller doses 20% vs. 4% in higher doses had normal periods after stopping therapy but more in 5 mg had heavy bleeding after stopping drug 20% in gp1vs30% in group 2, Thus evaluating all studies. Amenorrhea was observed as 90% with 10mg, 70-80mg with 5mg and 75% with 2.5 mg.

As far as the reduction in fibroid volume is concerned, reduction in median fibroid volume found in the present study after 3 months' treatment was 35.57% in patients receiving 2.5mg ulipristal acetate and 10.44% in those receiving 5mg ulipristal acetate.

The percentage reduction in the 5mg ulipristal group was lower than those reported in previous trials (PEARL I demonstrates 21.2% reduction in fibroid volume with 5mg and 12.3% reduction with 10mg in previous trial also reduction was less in higher dose. The retrospective study by Brun et al described a 36% reduction in fibroid volume after treatment with 5mg ulipristal acetate and Woznick et al, similarly, found a 45.6% reduction. This unexplained lesser reduction with higher doses is difficult to explain. Although exact mechanism remains unclear, chief author hypothesizes the possible reasoning behind it, may be more amenorrhea with higher doses led to less supply to fibroid so less efficacy on fibroid tissues. Or maybe the ulipristal effects on receptors of endometrium and fibroid indifferent ways. The difference in fibroid volume reduction found in our study and those studies quoted above can be attributed to the baseline fibroid size. In previous trial cut off was kept as 10 cm whereas there was no cut-off for maximum fibroid size at recruitment in our study. The larger fibroids in the group receiving 5mg Ulipristal acetate, responded minimally to treatment or grew in size. This finding is also supported by the study conducted by Brun et al, who observed that an initial fibroid size of >8cm is a risk factor for progression despite treatment.

Another factor which could contribute to the discrepancy in results in ethnicity. The PEARL trials and those conducted by Burn and Woznick took place in Caucasian populations. A result similar to our study was reported by Lee et al[11] who compared the effect of a 3 month course of 5mg Ulipristal acetate and Leuprolide acetate in 101 women from Seoul, Korea. The authors found that the median fibroid volume reduction after Ulipristal acetate treatment was 12.4% which was significantly lower. Ethnicity might play a role in the response to this drug.

In group 1, receiving 2.5mg ulipristal acetate, there was a reduction in median fibroid volume from 79.65 cm^3 to 51.3 cm^3 – a 35.58% reduction, which was significant (p=0.002). However, 3 months after completing treatment, median myoma volumes, although reduced, were not significantly different from the baseline. Among participant receiving 5mg ulipristal acetate, median fibroid volumes did not significantly differ from the baseline after completing treatment or 3 months after.

It is seen that fibroids with small baseline volumes reduced in size after treatment, in both groups. However, there are fibroids with large baseline volumes in Group 2, which responded poorly to treatment or grew in size, and may have skewed the results. Hence, a subgroup analysis was done to determine the

response of <100cm3 and >100cm^3 in volume, to treatment. 13/20 patients receiving 2.5mg ulipristal acetate and 11/20 patients receiving 5mg ulipristal acetate had fibroid volumes <100cm^3 at baseline, (p=0.250).

The authors found that in terms of control of heavy menstrual bleeding and pelvic pain, treatment with 2.5mg Ulipristal acetate for 3 months was comparable to treatment with 5mg. Ssignificant reductions in PBAC scores, 3 months after stopping treatment, was seen with both 5mg, ulipristal acetate, 60-65% of women in both groups were menorrhagia at this follow up. However, there were sustained reductions in pelvic pain in both groups even 3 months after cessation of treatment. In terms of fibroid volume, a significant reduction was found after treatment with 2.5mg ulipristal acetate but lesser with 5mg. This discrepancy is difficult to explain.

More baseline PBAC score (> 300) was associated with more rebound phenomenon. Larger volume of fibroid > 100cm^2 was showing more recurrence. There were no features of Liver toxicity with any dose but one case receiving 5 mg dose had transient elevation of liver enzyme after 3 months but reverted back in 3months time.

With the reports of hepatic impairment with Esmya (ulipristal acetate) and four cases of acute liver failure, the European Medical Association have advised suspension of ulipristal acetate for the treatment of uterine fibroids, pending safety review. Following the EMA recommendations, India, Philippines, Thailand, Malaysia, Singapore, Ireland Dubai were also directed the recall of the drug. Hence this trial provides critical information on the safety and efficacy of a lower dose for an effective treatment of uterine fibroids.

Limitations of the study

This study is limited by its small sample size, as recruitment was prematurely terminated following the temporary ban on the prescription of ulipristal acetate advocated by the RCOG. As there was no restriction to fibroid size, the effects of the drug on fibroid volume may be skewed by larger fibroids which grew despite therapy, especially in the 5 mg group.

CONCLUSIONS

To conclude, ttreatment with 2.5mg ulipristal acetate for 3 months is a feasible option in terms of symptoms control when compared to 5 mg dose. Rebound phenomenon is more with higher dose. With concerns of side effects with 5 mg dose, chief author suggests to give 2.5 mg dose as it can be safer option. Further larger well powered studies may be conducted with lower doses of ulipristal for fibroid management.

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