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Original Research Article

Effect of ulipristal acetate on leomyoma of uterus

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ABSTRACT

Background: The efficacy and side-effect profile of ulipristal acetate (UPA) for the treatment of symptomatic uterine fibroids before surgery are unclear. Main objective of the study to see the effect of UPA on leomyoma.
Methods: An observational clinical trial was conducted at the department of gynaecology and obstetrics, Sir Salimullah medical college and Mitford hospital, Dhaka, from January to June 2015. Thirty women aged 18-48 with symptomatic fibroid uterus were studied. They received Tablet UPA 5 mg/day for 3 months. Evaluation included history taking, physical examination, pelvic ultrasonography, and necessary investigations.
Results: The majority of patients (43.3%) were ≤30 years old. Before intervention, heavy bleeding was observed in all patients until the 8th day of menstruation. During intervention, majority had no bleeding from the 5th to 8th day, with only a few experiencing heavy bleeding on the 7th and 8th day. After intervention, most patients had no bleeding from the 5th to 8th day, with a few reporting spotting on the 5th day. Before treatment, 60% had fibroid size >10 cm^2. After treatment, 92.3% had fibroid size <10 cm^2, with 7.7% showing no fibroids. Mean uterine size decreased post-treatment. Majority (57.7%) had hemoglobin >11 gm/dl. Side effects included headache (11.5%), hot flashes (15.4%), and nausea/vertigo (19.2%). Treatment success rate was 86.7%.
Conclusions: In a group of selected patients with fibroid uterus and heavy menstrual bleeding, UPA (5 mg/day for 3 months) successfully decreases blood loss and shrinks fibroid and uterine size by 86.7%.

Keywords: UPA, Leomyoma, Uterus

INTRODUCTION

Uterine leomyomas are benign clonal neoplasms arising from smooth muscle cells in the uterine wall. Although the exact etiology of fibroids is not well established, it is known that these tumours depend on sex hormones for their growth. In addition to anemia caused by heavy bleeding, fibroids can cause pelvic pain, pressure, dysmenorrhea, reduced quality of life, and infertility. Current management strategies consist mainly of surgical or radiologic interventions, and options for medical therapy are limited.[1] These regimens are as effective as leuprolide acetate in controlling uterine bleeding and induce significant fever hot flashes. At though leuprolide

acetate induces significantly greater uterine volume shrinkage than UPA, the SPRM provides a more sustained effect on the reduction of myoma volume after discontinuation of treatment.[1] Treatment with 5 mg or 10 mg UPA for 13 weeks controls excessive bleeding and reduces total fibroid volume.[2] The median fibroid volume change was 45%. Amenorrhoea rates were 89%, 88% % and 90% for the 131,119 and 107 women who received treatment courses 2, 3, and 4 respectively. Median fibroid volume change from baseline was 63%.[3]

Acording to clinical data, UPA shows several advantages. It is faster than leuprolide in reducing the fibroid associated bleeding, it significantly improves haemoglobin and haematocrit levels in anaemic patients and it grants a significant reduction in the size of fibroids, which lasts for at least 6 months after the end of the treatment. It keeps oestradiol levels at mid follicular phase range, theirby reducing the incidence of hot flushes and exerting no impact on bone turnover.[4] There are several study about UPA. In one study patients were randomised to receive UPA 5 mg/day (96 women) or UPA 10 mg/day (98 women) or placebo (48 women). Finding showed that after 13 weeks, UPA controlled uterine bleeding in 91%, 92%, and 19% women receving UPA 5 mg, 10 mg, and placebo, respectively. Fibroid volume shrank by 21% in the 5 mg group and 12% in the 10 mg group but increased by 3% in the placebo group.[4] Uterine bleeding was controlled in 90% of patients receiving 5 mg of UPA, in 98% of those receiving 10 mg of UPA, and in 89% of those receiving leuprolide acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of UPA, 5 days for those receiving 10 mg of UPA, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5 mg of UPA, for 10% of those receiving 10 mg of UPA, and for 40% of those receiving leuprolideacetate.[1]

The role of progesterone in the proliferation of myomas has led to an increased interest in the modulation of the progesterone signaling pathway, SPRMs have a specific effect on the endometrium, with the antiproliferative effects leading to a reduction in bleeding volume or even, amenorrhoea *in vitro* and *in vivo*, UPA is a potent and selective modulator of progesterone receptor activity with effects on the progesterone receptors in the Myometrium and the endometrium. UPA inhibits ovulation without major effect on oestradiol formation and without an anti-glucocorticoid effect.[5] The spontaneous pregnancy after UPA to reduce fibroid size may support in the potential clinical utility of this SPRM in the management of women with pregnancy desire of uterine fibroid after a prior myomectomy. Patients who refuse a new surgical procedure and/or those who are going to undergo assisted reproductive techniques would benefit from UPA. It effectively shrinks fibroids, avoids risks of a new surgical producer, and allows an immediate attempt at conception after the end of treatment.[6] The objective of the present study is to see the effectiveness of UPA in shrinking large fibroids and control of bleeding.

Objective

General

General objectives were to see the effect of UPA (UPA) on leomyoma of uterus.

Specific

Specific objectives were to see the effectiveness of UPA in controlling bleeding in patients with fibroid uterus, to see the shrinking of fibroid after giving UPA and to see the side effects of UPA.

METHODS

Study design

An observational clinical trial; before-after trail study design was used.

Place of study

The study was carried out in the department of obstetrics and gynaecology, Sir Salimullah medical college and Mitford hospital, Dhaka.

Study period

Study conducted from January 2015 to June 2015.

Study type

A clinical trial study type was used.

Study population

Women of 18-48 years age were included in the study.

Sample size

Study showed for a change in health state level (Score on VAS range from 0 100, with higher score indicating a better heath state) of 15.6, standard deviation of 20.2, power of 95% and alpha error of 0.05. Mean and standard deviation were calculated for quantitative variables. A two-sided test was used with a 5% level of significance. The effect size is computed as:

$$ES = \frac{|\mu_1 - \mu_0|}{\sigma} = \frac{15.5}{20.2} = 0.77$$

Where,

μ1=67.9, μ0=83.4 and σ=20.2

The effect size represents the meaningful difference in the mean 15.5 and 20.2 standard deviation units different.

Now substitute the effect size and the appropriate Z values for the selected α and the power to compute the sample size.

$$n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{ES} \right)^2 = \left(\frac{1.96 + 1.64}{0.77} \right)^2 = 22$$

n=22

In addition, 8 cases were added and finally (n=22+8=30) 30 samples were ensured that a two-sided test with α =0.05 has 95% power to detect a 15.5 difference in mean health state level.

Sampling method

Purposive sampling i.e., who fulfills inclusion and exclusion criteria.

Inclusion criteria

Non-pregnant women of reproductive age with uterine fibroids <10 cm in diameter, experiencing menorrhagia, and a uterus size <16 weeks' gestation, seeking conservative treatment were included in study.

Exclusion criteria

Patient with bronchial asthma, renal disease, liver disease, cancer of the uterus, cervix, ovary, or breast, and severe anemia were excluded.

Uterine leomyomas

They are benign clonal neoplasms arising from smooth muscle cells in the uterine wall. They contain an increased amount of extracellular collagen and elastin.

UPA

It is a progesterone receptor modulator. It targets hormone balance by blocking the effect of progesterone.

Side effects of UPA

Hot flushes, headache, breast pain or tenderness, muscle, bone or joint pain, nausea, oedema and vertigo.

Procedures of preparing and organizing materials

Amount of bleeding, size of the fibroid, size of the uterus and side effects. All case record forms were checked very carefully to identify any error in collecting data. Data processing work consist of registration of schedules, editing, coding and computerization, preparation of dummy tables, analysis and matching data. The technical matter of editing, coding and computerization was done by self.

Procedures of collecting data

Thirty patients were taken for this study. The subject underwent history taking, physical examination, pelvic ultrasonography, and necessary investigation. Then tablet UPA 5 mg/day was administered for 3 months. All patients were followed up during and after completion of treatment. During treatment, each patient followed up monthly. At the end of each UPA treatment course, the time to onset of amenorrhoea for each treatment course was evaluated. Uterine bleeding was assessed by using a simplified semiquantitative bleeding scale which included four categories: "no bleeding", "spotting", "bleeding" or "heavy bleeding". The size of the fibroid and the size of the uterus were measured by USG. After completion of treatment, each patient was followed up after 1 month.

Quality assurance strategy

Statistical analysis was carried out by using the statistical package for social sciences version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated by frequencies and percentages. The procedure was followed strictly. Accuracy of data collection was ensured.

Ethical implications

For ethical clearance, the research proposal was submitted to the ethical committee of Sir Salimullah Medical College and Mitford Hospital, Dhaka. After the ethical committee approved this proposal, research protocol was submitted to BCPS. Written informed consent was obtained from the patients after explaining them about nature, objective, procedure, risks and benefits and implications of the study. The respondents were given assurance that the findings of the interview or investigation or examination were not used/disclosed to any unauthorized person or authority other than the research purpose. All study subjects were assured of adequate treatment of any complication developed in relation to study purpose. Privacy and confidentiality were strictly maintained.

RESULTS

Table 1 shows the distribution of the patient according the age group. The age ranged from 25-40 years and the maximum patients (43.3%) were in the age range of ≤30 years. The mean age of the patient was 30.0±4.6 years.

Table 1: Distribution of the study patients by age (n=30).

Age (in years)	N	%
≤30	13	43.3
31-35	7	23.3
>35	10	33.3
Mean±SD	30±4.6	
Range (min-max)	25-40	

Table 2: Distribution of the study patients by parity (n=30).

Parity	N	%
Nulli para	5	16.7
Multi para	25	83.3

Table 2 shows parity of the study patient, it was observed that majority (83.3%) patients were multi para and 5 (16.7%) were nulli para.

Assessment of menstrual bleeding during intervention of patients (Table 3). Observed that majority 26 (86.7%) patients had heavy bleeding during 1st day, 21 (70%) had heavy bleeding during 2nd day, 20 (66.7%) had moderate bleeding during 3rd day, 15 (50%) having spotting during 4th day and 4 (13.3%) had no bleeding. During 5-8th day majority patients had no bleeding. Only 2 (6.7%) during 7th day and 4 (13.3%) patients during 8th day had bleeding. So heavy bleeding during menstruation gradually decreased with UPA administration and 26 patients developed amenorrhea during intervention by day 8. For rest of study period when UPA was being administered, all 26 patients have amenorrhea. In 4 patients, where bleeding could not be controlled with UPA: They were dropped out and advised for surgical treatment (hysterectomy). There was treatment failure in 13.3% cases.

The mean percentage of bleeding decline 6.39±4.04% varied from 0-33.3% just after completion of treatment.

Table 4 shows assessment of menstrual bleeding after intervention of the patients. It was observed that out of 26 patients, all (100.0%) patients having moderate bleeding after intervention in 1st day, 26 (100.0%) having moderate bleeding in 2nd day, 13 (50.0%) having spotting and 13 (50.0%) had moderate bleeding in 3rd day, 13(50.0%) having spotting in 4th day and 11 (42.3%) were no bleeding. In 5th day, 6th day, 7th day and 8th day majority patients had no bleeding. After inter venation only 2 (7.7%) having spotting on 5th day.

Table 5 shows size of the fibroids of the patients. It was observed that before treatment size of the fibroid was measured in 30 patients. Among them majority 18 (60.0%) had fibroid size >10 cm^2 (60%). Four patients couldn't complete the treatment cycle, because of uncontrolled bleeding and anaemia. Subsequently they underwent hysterectomy. Just after completion of treatment 24 (92.3%) patients had fibroids size <10 cm^2 and in 2 (7.7%) patients no fibroid was found. One month after completion of treatment 24 (92.3%) had fibroid size <10 cm^2 and in 2 (7.7%) patients' fibroids totally disappeared. Mean size of the fibroid was 17.48±3.62 cm^2 before treatment and 3.76±0.46 cm^2 just after completion of treatment. The mean size of the fibroids was statistically significantly ($p<0.05$) reduced Just after completion of treatment.

The mean percentage of size of fibroids declined 69.8±16% (Range 30.3-89.3%) just after completion of treatment.

Table 3: Distribution of the study patients by assessment of menstrual bleeding during intervention (n=30).

Days	N	Pattern of bleeding during intervention							
		No bleeding		Spotting		Moderate		Heavy	
		N	%	N	%	N	%	N	%
1st day	30	0	0.0	0	0.0	4	13.3	26	86.7
2nd day	30	0	0.0	2	6.7	7	23.3	21	70.0
3rd day	30	0	0.0	4	13.3	20	66.7	6	20.0
4th day	30	4	13.3	15	50	9	30.0	2	6.7
5th day	26	17	56.7	9	30	0	0.0	0	0.0
6th day	26	26	100.0	0	0.0	0	0.0	0	0.0
7th day	26	24	80.0	0	0.0	0	0.0	2	6.7
8th day	26	22	73.3	0	0.0	0	0.0	4	13.3

*4 patients dropped out as bleeding was not controlled and all of them underwent hysterectomy.

Table 4: Distribution of the study patients by assessment of menstrual bleeding after intervention (n=26*).

Days	N	Pattern of bleeding after intervention							
		No bleeding		Spotting		Moderate		Heavy	
		N	%	N	%	N	%	N	%
1st day	26	0	0.0	0	0.0	26	100.0	0	0.0
2nd day	26	0	0.0	0	0.0	26	100.0	0	0.0
3rd day	26	0	0.0	13	50	13	50.0	0	0.0
4th day	26	11	42.3	13	50	2	7.7	0	0.0
5th day	26	24	92.3	2	7.7	0	0.0	0	0.0
6th day	26	26	100.0	0	0.0	0	0.0	0	0.0
7th day	26	26	100.0	0	0.0	0	0.0	0	0.0
8th day	26	26	100.0	0	0.0	0	0.0	0	0.0

*4 patients dropped out as bleeding was not controlled and all of them underwent hysterectomy.

Table 5: Distribution of the study patients by size of the fibroids (n=30)

Size of the fibroids (cm^2)	Before treatment, (n=30)		Just after completion of treatment, (n=26*)		One month after completion of treatment, (n=26*)	
	N	%	N	%	N	%
<10	12	40.0	24	92.3	24	92.3
>10	18	60.0	0	0.0	0	0.0
No fibroids	0	0.0	2	7.7	2	7.7
Mean ± SD	17.48±3.62		3.76±0.46			
P value	0.001[s]					

P value reached from paired t test, *4 patients dropped out as bleeding was not controlled and all of them underwent hysterectomy

Table 6: Distribution of the study patients by size of the uterus (n=30).

Size of the uterus (cm^2)	Before treatment, (N=30)		Just after completion of treatment (N=26*)		One month after completion of treatment (N=26*)	
	N	%	N	%	N	%
<25	10	33.3	15	57.67	15	57.7
25-40	11	36.7	10	38.5	10	38.5
>40	9	30.0	1	3.8	1	3.8
Mean ± SD	34.0±14.6		26.2±5.9		26.1±5.8	
Range (min-max)	21.0-88.4		21.0-44.6		21.0-44.6	
P value	0.001[s]					

P value reached from paired t-test, * 4 patients dropped out as the bleeding was not controlled and all of them underwent hysterectomy.

Table 6 shows the size of the uterus of the patients. It was observed that before treatment uterine size was measured in 30 patients. Among them majority 10 (33.3%) had uterus size <25 cm^2. Just after completion of treatment 15(57.7%) patients continued to have uterine size <25 cm^2. One month after completion of treatment 15 (57.7%) patients had uterus size <25 cm^2. Mean uterus size was found 34.0±14.6 cm^2 before treatment, 26.2±5.9 cm^2 in just after completion of treatment and 26.1±5.8 cm^2 one month after completion of treatment. The mean size of the uterus was statistically significantly reduced ($p<0.05$) Just after completion of treatment.

The mean percentage of size of the uterus declined (16.9±3.28% range from 0-49.6%) after completion of treatment. Table 7 shows the side effects of UPA. It was observed that out of 26 patients, 12 (46.1%) patients had some minor side effects. Among them 03 (11.5%) had headache, 5 (19.2%) had nausea/ vertigo and 4 (15.4%) had the hot flashes.

Table 7: Distribution of the study patients by side effects of UPA (n=26*).

Side effects	N	%
Hot flashes	4	15.4
Headache	3	11.5
Nausea/vertigo	5	19.2
No complaints	14	53.99

* 4 patients dropped out as bleeding was not controlled and all of them underwent hysterectomy.

Table 8 shows outcome of the patients. It was observed that 26 (86.7%) patients were treated successfully with UPA treatment and in 4 (13.3%) patients there was UPA failure with treatment. Hysterectomy was done in 4 (13.3%) patients due to uncontrolled bleeding.

Table 8: Outcome of the UPA treatment in patients with fibroid uterus and menorrhagia (n=30).

Outcome	N	%
Success	26	86.7
Failure	4	13.3
Hysterectomy done	4	13.3

All 4 patients underwent hysterectomy.

DISCUSSION

This clinical trial was carried out with an aim to see the effectiveness of UPA in controlling bleeding in patients with fibroid uterus and see the shrinking of fibroid after giving UPA and also to see the side effect of UPA. Non-gravid women with, the size of the fibroid <10 cm diameter and size of the uterus <16 weeks gestation was enrolled in this study. Post-menopausal women, size of fibroid >10 cm diameter, size of the fibroid uterus >16 weeks gestation, bronchial asthma, renal disease, liver disease, cancer of the uterus, cervix, ovary or breast and severe anaemia were excluded from the study. The present study findings were discussed and compared with previously published relevant studies. Uterine fibroids (or myomas) are monoclonal tumors of the smooth muscle cells of the uterus. They are considered the most common benign tumors of the female genital tract, as they are clinically apparent in up to 25% of women irrespective of their age. Moreover, they occur in up to 30-40% of women over the age of 40 years.[7] The reported incidence ranges from 30% to 70% in premenopausal women and increases with age.[8]

In this present study it was observed that the age ranged from 25-40 years and the maximum patients (43.3%) were in the age range of ≤30 years. The mean age of the patient was 30.0±4.6 years varied from 25-40 years. A study carried out in the USA with randomly selected women between the ages of 35 and 49 years (who were screened by self-report, medical record, and sonography) showed that the incidence of uterine fibroids by age 35 was 60% among African-American women, increasing to >80% by age 50, whereas Caucasian women showed an incidence of 40% by age 35, and almost 70% by age 50 observed by day.[9] African-American women usually become clinically symptomatic fibroid uterus at least 4 years earlier than Caucasian women-the peak is between the ages of 30 and 50 (38/10,000 vs 16/10,000 women).[10,11] Which are comparable with the current study. Bleeding was assessed using a semiquantitative bleeding scale. For an exploratory endpoint, the pictorial blood-loss assessment chart (PBAC) was used to assess the magnitude of menstrual bleeding over 8 days at baseline (start of the first treatment course) and for the first menstruation after the end of each treatment course. A score greater than 100 indicates HMB.[3,12]

In this series it was observed that 4 underwent hysterectomy and out of 26 patients, all (100%) patients having heavy bleeding after intervention in 1st day, 26 (100.0%) having heavy bleeding in 2nd day, 13 (50.0%) having spotting and 13 (50.0%) had moderate bleeding in 3rd day, 13(50.0%) having spotting in 4th day and 11(42.3%) were no bleeding. In 5th day, 6th day, 7th day and 8th day majority patients were no bleeding. Only 2(7.7%) having spotting after intervention in 5th day.[3] In another study mentioned that early reports of the use of mifepristone for the treatment of fibroids date back to 2002, when used doses ranging from 12.5 to 50 mg daily and reported a reduction in uterine/fibroid volume of 40-50%, with amenorrhea in most subjects.[13,14] This report was corroborated by a paper a year later from a group who used mifepristone at a dose of 5 or 10 mg per day for 1 year and found that it was effective in decreasing mean uterine volume by 50%, while amenorrhea occurred in 40-70% of the subjects.[15] In this current study it was observed that before treatment uterus size measured in 30 patients among them majority 11 (36.7%) had uterus size 25-40 cm^2 and 4 patients dropped-out due to undergoing hysterectomy. Just after completion of treatment 15 (57.7%) patients had uterus size <25 cm^2. One month after completion of treatment 15 (57.7%) patients had uterus size <25 cm^2. Mean uterine size was found 34.0±14.6 cm^2 before treatment, 26.2±5.9 cm^2 just after completion of treatment and 26.1±5.8 cm^2 one month after completion of treatment. The above findings indicate that uterine size declined in subsequent follow up from the before treatment[4.]

UPA is an orally active synthetic SPRM, characterized by a tissue-specific partial progesterone antagonist effect.[16] Progesterone normally promotes fibroid growth in two ways: on the one hand, it up regulates epidermal growth factor (EGF) and Bcl-2 gene, on the other hand it down regulates the tumor necrosis factor gene (TNF). UPA, as a progesterone antagonist, inhibits the proliferation of leiomyoma cells and induces apoptosis by increasing cleaved caspase-3 expression and decreasing Bcl-2 expression.[17] Moreover, UPA down regulates the expression of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and their receptors. Thus, it suppresses neo-vascularization, cell pro-liberation, and survival in leiomyoma cells but not in normal myometrial cells.[18] Additionally, UPA increases the expression of matrix metalloproteinases (MMPs) and decreases the expression of tissue inhibitor of metalloproteinases (TIMPs) and collagens in cultured fibroid cells. Thus, UPA may impair fibroid tissue integrity by reducing the deposition of collagen in the extracellular spaces.[19] Investigated the efficacy and safety of repeated 12-week courses of 5 or 10 mg daily of UPA for intermittent treatment of symptomatic uterine fibroids. A total of 451 patients with symptomatic uterine fibroid(s) and heavy bleeding.[20]

Limitations

The present study was conducted at a very short period of time.

Small sample size was also a limitation of the present study. Therefore, in future further study may be under taken with large sample size. The period of follow up was short and only one treatment cycle was proceeded. The follow-up period should be longer and multiple courses of UPA maybe required for successful treatment.

CONCLUSION

This study was undertaken to see the effect of UPA on leomyoma. Majority patients having heavy bleeding during 1st day and 2nd day and after intervention all patients had moderate bleeding during 1st day and 2nd day. Size of the fibroids and size of the uterus declined in subsequent follow up after treatment. After treatment with UPA most of the patients had no complaints. However, nausea/vertio, headache and hot flashes observed within 20.0% of the patients. Success and treatment failure were observed 86.7% and 13.3% respectively. In a group of selected patients of fibroid uterus with excessive menstrual bleeding, (UPA 5 mg/day for 3 months) can statistically significantly reduce the bleeding, size of the fibroid, and size of the uterus in 86.7% of cases. There were minimal side effects like headache, hot flushes, nausea and vertigo.

Recommendations

UPA may be used as first line treatment for patients with fibroid uterus with symptoms who desires conservative treatment. Further the large, controlled studies (RCT) can be undertaken by including large number of patients and prolonged follow-up and/or multiple treatment courses.

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