Ulipristal Acetate: A New Hope in the Conservative Management of Uterine Fibroid

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ABSTRACT

Introduction: Uterine fibroid is the most common benign tumor of female reproductive tract during reproductive life. Currently medical management of fibroid are limited to preoperative indications to decrease the size and vascularity of fibroid. Ulipristal acetate (UPA) is a promising alternative to treat symptomatic fibroid. It controls excess bleeding and reduces myoma size and uterine volume. Study aimed at evaluation of the Ulipristal acetate (UPA) effectiveness in women with the uterine fibroid

Material and methods: This study was conducted from February 2016 to June 2017. Total number of cases enrolled in this study was 50. Three months course of Ulipristal Acetate 10mg daily were given. Three such courses were given. In between every course a gap of one full menstrual cycle was given. Evaluation was done at the end of each course and finally 3 months after the 3rd course.

Results: In our study maximum patients (52%) were in the age group 30-40 years. Maximum parity was 4 (28) and 12 patients were nulliparous. Most predominant symptoms were menorrhagia and pain (56%). After the end of course 3, 48 patients had fibroid volume reduction ≥25% and 42 patients developed amenorrhoea. There were no serious side effects of UPA noted in the entire treatment course. Hot flushes, headache, abdominal pain and nasopharyngitis were minor complaint.

Conclusion: UPA, 10mg, once daily dose is effective in decreasing menstrual blood loss, reducing fibroid volume and pain in women with symptomatic uterine fibroid.

Keywords: Menorrhagia, Amenorrhoea, Endometrium

INTRODUCTION

Uterine fibroid is the most common benign tumor of female reproductive tract[1] during reproductive life. Scientific name of fibroid is leiomyoma. It represents one of the most frequent indications for hysterectomy in premenopausal women. At any given time, nearly 15.25 million women have fibroids in India.[2] It constitutes a major public health cost.[3]

The most common symptoms are heavy menstrual bleeding, pelvic pressure symptoms, pain of varying degree and type. Surgical and other invasive interventions are still the main stay of treatment with associated complications.[4] Currently medical management of fibroid are limited to preoperative indications to decrease the size and vascularity of fibroid. Till now no medical therapy is there to provide long term efficacy and acceptable tolerability and safety.

Ulipristal acetate (UPA) is a selective P receptor modulator (SPRM). It has proapoptotic and antiproliferative effect on fibroid cells. At the same time it does not suppress estradiol (E_2) to non physiologic levels. It has potent ability to modulate progesterone activity and a welcome pharmacokinetic property which allow it for single daily dose schedule. In cases of symptomatic uterine fibroid, it is efficient to control excess bleeding.[5,6] It also reduces myoma size and uterine volume found to be maintained for at least 6 months in patients not undergoing surgery. Use of SPRM induces a number of changes in endometrium. These changes spontaneously reverse over a period of several weeks to months after cessation of UPA therapy.[7] Study aimed at evaluation of the Ulipristal acetate (UPA) effectiveness in women with the uterine fibroid

MATERIAL AND METHODS

This study was conducted from February 2016 to June 2017. Total number of cases enrolled in this study was 50.

Inclusion criteria

1. Women 25-48 years old with symptomatic uterine fibroid.
2. Pictorial Blood loss Assessment Chart (PBAC) score >100 during days 1-8 of menstruation.
3. At least one fibroid of 3-10cm.
4. Size of fibroid >14 weeks of gestation.
5. BMI 20-40.
6. Menstrual cycles of 20-40 days with serum Follicle Stimulating Hormone (FSH) level <20IU/ml.

Exclusion criteria

1. Significant finding on pap smear test within 12 months.
2. History of or current uterine, cervical, ovarian or breast malignancy.
3. Endometrial hyperplasia or adenocarcinoma within past 6 months.
4. Calcified fibroid.
5. Ovarian cyst> 4cm in ultrasound.
6. Large uterine polyp (>2cm).

Three months course of Ulipristal Acetate (UPA) 10mg daily were given. Three such courses were given. In between every course a gap of one full menstrual cycle was given.

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At the end of every course amenorrhoea, improvement in menorrhagia, reduction in fibroid volume and symptom improvement (mainly pain) was noted. Evaluation was done at the end of every 3 months course and finally 3 months after the completion of all three courses.

Following points were evaluated:

1. Occurrence of amenorrhoea at the end of each UPA course. Amenorrhoea was defined as no bleeding for a continuous period of at least 35 days. (Spotting of 1 day was ignored within a period of 35 days).
2. Bleeding was assessed using a semi quantitative bleeding scan. The Pictorial Blood Loss Assessment Chart (PBAC) was used to assess the magnitude of menstrual bleeding over 8 days at baseline and for the first menstruation after the end of each treatment course. A score greater than 100 indicates heavy menstrual bleeding.
3. Reduction in the size of fibroid using transvaginal sonography.
4. Relief of pain: measured with short form Mc Gill pain questionnaire.
5. Adverse events (if any) known by:
   a. Vital signs: pulse, blood pressure, respiratory rate.
   b. Physical examination.
   c. Gynaecological examination.
   d. Breast examination.
   e. Electrocardiogram
   f. Hematology- Complete blood count, coagulation profile, lipid profile, liver function test, serum TSH, serum prolactin, serum ACTH, serum estradiol level.
   g. Ovarian ultrasound.
   h. Changes from baseline in endometrial thickness by transvaginal sonography.
   i. Clinically significant changes in endometrial biopsy. Endometrial biopsy was taken 3 months after the last course of UPA.

The proportion of women attaining amenorrhoea at the end of each UPA treatment course and the time of onset of amenorrhoea at the end of each UPA treatment course were evaluated. The volume of largest fibroid was assessed using transvaginal sonography. The same fibroids identified during screening were followed throughout the study. Also uterine volume, ovaries, endometrial thickness and uterine cavity was evaluated using TVS at baseline, at the end of UPA treatment course 1, course 2 and approximately 3 months after the end of final treatment course 3.

STATISTICAL ANALYSIS

Descriptive statistics like mean and percentages were used to interpret data with the help of Microsoft office 2007.

RESULTS

In our study maximum patients (52%) were in the age group 30-40 years followed by 32% in the age group 40-48 years and minimum number (12%) in the age group 24-30 years (table 1). Maximum parity was 4 (28) and 12 patients were nulliparous. Most predominant symptoms were menorrhagia and pain (56%). Only menorrhagia as a presenting symptom was present in 16%, pain only in 4% and pressure symptoms in 8% (predominantly urinary symptom). The effect of UPA after 1st treatment course is shown in table 2. Effect of UPA on fibroid volume is shown in table 3. In three cycles of UPA, fibroid continued to shrink. In TVS, this volume reduction was mostly found to be maintained 3 months after the final treatment course. There was improvement in pain noted third week onward which was maintained throughout UPA course and 3 months after the completion of course. Menstrual bleeding(PBAC days 1-8) was reduced from median of PBAC score 210 and 242 at the start of first course to 59 and 18 after the end of 3rd UPA course. After the first 3 months course, 2 patients discontinued the treatment because of the cost of the treatment. No cases of endometrial hyperplasia or adenocarcinoma were reported. In 6% of cases transient increase in endometrial thickness was noted which subsided 3 months after completion of course. There were no serious side effects of UPA noted in the entire treatment course. Hot flushes, headache, abdominal pain and nasopharyngitis were minor complaint (table 4). There were no significant changes noted in physical examination, vital signs, liver function

Age (yrs)	No. of patients	Percentage (%)
20-30	6	12
30-40	26	52
40-48	18	36
Total	50	100

Table-1: Age Distribution of patients

Assessment	No. of patients	Percentage(%)
Amenorrhoea	36	72%
No. of women with spotting	35	70%
Percentage change in volume of fibroid (total reduction ≥5%)	39	78%
Uterine volume (percentage reduction from baseline) reduction ≥25%	28	56%

Table-2: Evaluation after first treatment course of Ulipristal acetate

Treatment course	No. of patients with Fibroid volume reduction ≥25%	No. of patients developing amenorrhoea	Total no. of patients taking treatment
Course 1	39	36	50
Course 2	44	39	48
Course 3	48	42	48

Table-3: Evaluation of women in amenorrhoea and fibroid volume reduction ≥25% at rhe end of each treatment course

Side effects	No. of patients	Percentage (%)
Headache (mild)	11	22
Hot flushes	8	16
Nasopharyngitis	7	14
Abdominal pain (mild)	14	28

Table-4: Evaluation of minor side effects

tests, hormone levels and other laboratory tests, ECG and ovarian ultrasound.

DISCUSSION

None of the currently existing medical therapy options offer a significant breakthrough in fibroid management. Surgical options require skill, is costly and fertility prospect is uncertain. Gonadotrophin releasing hormone (GnRH) analogues were the only drugs available for preoperative treatment of uterine fibroid till date. But their use was associated with several side effects like suppressed estrogen level which induces post menopausal symptoms and fibroid quickly return to their previous size after cessation of treatment.[8] Bone loss is also significant. Role of levonorgestrel releasing intrauterine device is not consistent and is contraindicated in distorted uterine cavity and submucous fibroids.[9] So clearly there is a need for medical therapy that eliminates the need for surgery or postpones surgery and has efficacy equivalent to or superior to surgery and superior to surgery and should also offer a relatively cheaper alternative. Today UPA is the most effective medication for conservative treatment of uterine fibroid.[10] It is approved by European Union in 2012 and Health Canada in 2013 for preoperative treatment of moderate to severe symptoms of uterine fibroid. Intermittent, repeated course of UPA induces high rate of amenorrhoea in our study, thus confirming its ability to control menorrhagia which is the commonest and most troublesome symptom. Also our results further confirm the shrinking effect of UPA on fibroid volume with repeated cycle. Our study further reconfirms no rapid rebound growth after three months of cessation of UPA treatment. At the end of treatment and three months thereafter, reduction in fibroid volume and improvement in pain were mostly maintained. Thus our results reconfirm and reendorse that repeated, intermittent treatment with UPA could become the first long term medical option for symptomatic uterine fibroid by inducing apoptosis and decreasing proliferation in fibroid cells.[11] The percentage of subjects with endometrial thickness ≥16mm was small 8% after 1st treatment course and returned to normal or below screening level in subsequent treatment courses. The changes that are observed are reversible after treatment cessation and are called "Progesterone receptor modulator associated endometrial changes" and should not be confused with endometrial hyperplasia. There are some limitations of our study. First it was a very small study (only 50 cases). Second we could not use the placebo. However in previous studies it was concluded that UPA was superior to placebo and not inferior to GnRH agonist for control of heavy menstrual bleeding.[5,6] With UPA estrogen levels are more or less kept within normal range, fewer incidence of hot flushes was noted and there was no impact on bone turnover

CONCLUSION

UPA, 10mg, once daily dose is effective in decreasing menstrual blood loss, reducing fibroid volume and pain in women with symptomatic uterine fibroid. But a large study is still required to prove and confirm its safety. In case of repeated, intermittent, long treatment, periodic monitoring of endometrium is recommended.

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