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Original Research Article

Role of Ulipristal Acetate in the Conservative Management of Uterine Fibroid

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Abstract:

Background: 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

Methods: This study was conducted from October 2017 to February 2019 at Obstetrics & Gynaecology Department of Darbhanga Medical College and Hospital, Laheriasarai, Bihar. 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 two 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 (60%) were in the age group 30-40 years. Maximum parity was 4 and 12 patients were nulliparous. Most predominant symptoms were menorrhagia and pain (66%). After the end of course 3, 48 patients had fibroid volume reduction ≥25% and 41 patients developed amenorrhoea. Out of 12 patient who were nulliparous 10 patient complained of infertility, out of which 8 patients conceived after 3 complete course of treatment resulted in 6 live birth and 2 early miscarriages There were no serious side effects of UPA noted in the entire treatment course. Hot flushes, headache, abdominal pain and nasopharyngitis, nausea and dizziness 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 and it also improves fertility.

Keywords: Menorrhagia, Amenorrhoea, Endometrium.

Introduction

Uterine fibroids are the most common benign uterine tumours in women in the reproductive age group. They were first described in 1791 by Matthew Baillie of St. George's Hospital in London. They are also known as myomas or leiomyomas and occur in 20-50% of women. Atanygiven time15.25 million woman have fibroids in India Symptoms may vary and include dysmenorrhoea, heavy and prolonged menstrual bleeding, anaemia, pelvic pain and pressure, infertility, and recurrent miscarriages and may result in reduction of quality of life.

Many different management strategies are used, such as surgical treatment (myomectomy/hysterectomy by laparoscopy/ laparotomy/hysteroscopy, uterine artery embolization), nonsurgical procedures (uterine artery embolisation, MRI-guided focused ultrasound) as well as medical therapy. The choice of the appropriate treatment technique is made on the basis of many factors such as fibroid location, patient's age, the wish to preserve fertility, concomitant diseases, and the patient's preferences. Hysterectomy remains the most common treatment option because it is the only definitive treatment, and it eliminates the possibility of recurrence.

Medical therapy with progestins, progestin-releasing intrauterine devices, and gonadotropin-releasing hormone agonists (GnRHa) are also approved. Pharmacological treatments such as gonadotropin-releasing hormone agonists and antagonists have been used with only partial success. Countless side effects (including bone loss and hot flushes) and limited clinical effect decreased their role and

exposed a need for new effective medical treatments. Treatment with selective progesterone receptor modulators (ulipristal) has shown promising results with shrinkage of uterine leiomyomas and a prolonged clinical effect.

Ulipristal acetate (UPA) is a selective PROGESTERONE receptor modulator (SPRM). It has proapoptotic and antiproliferative effect on fibroid cells. At the same time it does not suppress estradiol (E2) 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. 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 October 2017 to February 2019 at Obstetrics and Gynaecological Department of Darbhanga Medical College & Hospital, Laheriasarai, Bihar.

Total number of cases enrolled in this study was 50.

Inclusion criteria

1. Women 20-45 years old with symptomatic uterine fibroid.
2. Patients having symptoms like menorrhagia, dysmenorrhea, abdominal pain, infertility, or any other symptoms related to fibroid
3. At least one fibroid of 3-8cm.
4. BMI 20-40
5. Pictorial blood loss assessment chart (PBAC) score>100
6. Patient having consented to be part of study

Exclusion criteria

1. Pregnant female
2. Those who refused consent
3. Renal or hepatic disease or any other condition in which ulipristal is contraindicated
4. Patient having adenomyoma, endometrial hyperplasia, genital tract infection
5. History of or current uterine, cervical, ovarian or breast malignancy
6. Not taken any previous medication

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

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.

Table 1: Age Distribution of patients

Age (yrs)	No. of patients	Percentage (%)
20-30	8	16
30-40	30	60
40 -45	12	24
Total	50	100

Table 2: Evaluation after first treatment course of Ulipristal acetate

Assessment	No. of patients	Percentage
Amenorrhoea	38	76
No. of women with spotting	36	72
Uterine volume (percentage reduction from baseline) reduction ≥25%	37	74

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

Treatment course	No. of patients with Fibroid volume reduction ≥25%	No. of patients developing amenorrhoea	Total no. of patients taking treatment Course
1	37	38	50
2	43	40	48
3	48	41	48

Table 4: Uterine volume (percentage reduction from the baseline) reduction after each treatment course

Percentage reduction	>50	>55	>60
Course1	30	28	25
Course2	35	32	30
Course3	39	38	36

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.

Results

In our study maximum patients (60%) were in the age group 30-40 years followed by 24% in the age group 40-45 years and minimum number (16%) in the age group 20-30 years (table 1). Maximum parity was 4 and 12 patients were nulliparous. Most predominant symptoms were menorrhagia and pain (66%)). Out of 12 patient who were nulliparous 10 patient complained of infertility, out of which 8 patients conceived after 3 complete course of treatment resulted in 6 live birth and 2 early miscarriages. 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. Percentage reduction of fibroid volume after each course of treatment is shown in table 4. 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 212 and 242 at the start of first course to 58 and 19 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 8% 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, nausea and dizziness were minor complaint (table 4). There were no significant changes noted in physical examination, vital signs, liver function side effects.

Table 5: Evaluation of minor side effects

Side effect	No. of patient	percentage
Headache %	10	20
Hot flushes	6	12
nasophyrangitis	5	10
Abdominal pain	12	24
Nausea and dizziness	8	16

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. 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.

The PEARL (PGL4001 Efficacy Assessment in Reduction of symptoms because of uterine Leiomyomata) I and PEARL II trials were published in 2012 when 5 mg UPA obtained European approval to be used for three-month preoperative treatment of women with uterine fibroids.

PEARL I was a randomised, double-blind, placebo-controlled trial evaluating three-month treatment with UPA (tablets with 5 or 10 mg UPA daily) in women with symptomatic fibroids, heavy uterine bleeding, and anaemia. The study results have shown that after 13 weeks, uterine bleeding was under control in 91% of women receiving 5 mg UPA, 92% of women receiving 10 mg UPA, but only in 19% of women receiving a placebo. Most patients achieved improvement of anaemia (haemoglobin> 12 g/dl) by the end of the three-month treatment period with UPA. It has been well documented that preoperative anaemia, even in a mild degree, is associated with increased risk of morbidity and mortality in patients undergoing surgery.

PEARL II compared 5 and 10 mg UPA with the standard medical treatment with GnRH (3.75 mg leuprolide acetate depot injection once monthly). The findings of this study demonstrated that uterine bleeding was controlled in 90% of patients receiving 5 mg UPA, 98% of patients receiving 10 mg UPA, and 89% of patients receiving leuprolide acetate. The median times to controlled bleeding were five to seven days for patients receiving UPA (5 and 10 mg, respectively), and 21 days for patients receiving leuprolide acetate.

Follow-up in a group of women who did not undergo surgery after the three-month UPA treatment showed that UPA had a sustained effect (up to six months) after the end of treatment. The PEARL III study was designed to estimate the efficacy and safety of long-term intermittent open-label three-month courses of 10 mg/day UPA for the treatment of symptomatic uterine fibroids. After the first UPA course, amenorrhoea occurred in 79% of women. Amenorrhoea rates were, respectively, 89, 88, and 90% in women who received two, three, and four treatment courses. The median time to amenorrhoea was 3.5 days from the start of treatment.The median fibroid volume reduction from the baseline was 49.9, 63.2, 67.0, and 72.1% after one, two, three, and four courses of treatment, respectively.

All endometrial biopsies showed benign histology without hyperplasia. PEARL III has demonstrated that administration of more than one course of UPA maximises the potential benefits of treatment when it comes to bleeding control and fibroid volume reduction.

PEARL IV evaluated the efficacy and safety of repeated 12-week courses of 5 or 10 mg UPA daily for intermittent treatment of symptomatic uterine fibroids. After the second treatment course, the median reduction in fibroid volume from the baseline was 54 and 58% in patients receiving 5 and 10 mg UPA, respectively. Improvement of pain and quality of life has been observed. Pregnancies after UPA treatment have been reported. Twenty-

one women wanted to conceive – obtaining 18 pregnancies, which resulted in 12 births of 13 healthy babies and six early miscarriages.

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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