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RESEARCH ARTICLE

ULIPRISTAL ACETATE VERSUS PLACEBO FOR FIBROID TREATMENT

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Abstract

Background: The efficacy and safety of oral ulipristal acetate for the treatment of symptomatic uterine fibroids before surgery are uncertain.
Methods: We randomly assigned women with symptomatic fibroids, excessive uterine bleeding (a score of >100 on the pictorial blood-loss assessment chart [PBAC, an objective assessment of blood loss, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding]) and anemia (hemoglobin level of ≤10.2 g per deciliter) to receive treatment for up to 13 weeks with oral ulipristal acetate at a dose of 5 mg per day (96 women) or 10 mg per day (98 women) or to receive placebo (48 women). All patients received iron supplementation. The coprimary efficacy end points were control of uterine bleeding (PBAC score of <75) and reduction of fibroid volume at week 13, after which patients could undergo surgery.
Results: At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5 mg of ulipristal acetate, and 19% of those receiving placebo (P<0.001 for the comparison of each dose of ulipristal acetate with placebo). The rates of amenorrhea were 73%, and 6%, respectively, with amenorrhea occurring within 10 days in the majority of patients receiving ulipristal acetate. The median changes in total fibroid volume were −21%,, and +3% (P = 0.002 for the comparison of 5 mg of ulipristal acetate with placebo. Serious adverse events occurred in one patient during treatment with 5 mg of ulipristal acetate (uterine hemorrhage) and in one patient during receipt of placebo (fibroid protruding through the cervix). Headache and breast tenderness were the most common adverse events associated with ulipristal acetate but did not occur significantly more frequently than with placebo.
Conclusions: Treatment with ulipristal acetate for 13 weeks effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids.

Introduction:-

Uterine leiomyomas, or fibroids, are benign, hormone-sensitive, smooth-muscle tumors that occur in 20 to 40% of women of reproductive age.1,2 The most common symptoms are menorrhagia and iron-deficiency anemia, which may lead to chronic fatigue3 that may not be adequately controlled with iron supplementation alone.4-6 Other symptoms include pelvic pain, dysmenorrhea, and pressure effects, which may adversely affect quality of life and fertility.7-10 Many patients require intervention, and the choice of treatment is guided by the patient's age and

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desire to preserve fertility and avoid hysterectomy.10 Fibroids are the most common indication for hysterectomy.1 Other treatments include myomectomy, hysteroscopic removal, uterineartery embolization, and various other interventions performed under radiologic guidance.10,11 Medical therapies are also available, but these therapies have limitations. Gonadotropin-releasing hormone (GnRH) agonists can be used as bridging or presurgical treatments and create an artificial menopausal state, resulting in reversible reduction of uterine and fibroid volume and aiding in the correction of anemia12-16; however, GnRH agonists frequently cause hot flashes, and the use of these drugs is approved only for short-term therapy because of safety concerns (loss of bone mineral density). Progestins are often associated with breakthrough bleeding that limit their use,17 and they may promote proliferation of fibroids.18-21 The levonorgestrel-releasing intrauterine system can be used in patients who do not have large uteri distorted by fibroids, but irregular bleeding is frequent, expulsion of the intrauterine device is more common than in women without fibroids, and the effect on fibroid volume is controversial.22 The role of progesterone in promoting the growth of fibroids has stimulated interest in modulating the progesterone pathway. Results from small pilot studies and other uncontrolled trials in which selective progesterone-receptor modulators such as asoprisnil, mifepristone, telapristone, and ulipristal acetate were used have suggested the potential benefit of these agents in patients with fibroids.23-26 Ulipristal acetate is a selective progesteronereceptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antiglucocorticoid activity.27,28 In two small, phase 2 studies (one involving 18 patients and one involving 38 patients), a 3-month course of ulipristal acetate at a dose of 10 mg per day or 20 mg per day reduced abnormal bleeding and significantly decreased fibroid volume; there was no advantage of the 20-mg dose over the 10-mg dose. We conducted the PGL4001 (Ulipristal Acetate) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL I) trial to determine the effects of 5 mg of ulipristal acetate per day and 10 mg of ulipristal acetate per day on uterine bleeding and fibroid volume in women with symptomatic fibroids who were planning to undergo surgery

Adverse Effects And Complications

The common adverse effects associated with UPA include gastrointestinal symptoms such as nausea and vomiting and less commonly dry mouth, appetite disorders, diarrhoea, flatulence, altered taste, dry throat and thirst. Other effects include headaches, back pain, pelvic pain, myalgia, breast tenderness, fatigue, menstrual cycle irregularity, altered mood and dizziness. The unusual or uncommon side effects include fever, chills, hot flashes, increased risk of infection, malaise, anxiety, drowsiness, impaired concentration, insomnia, vision disorders, loss of libido, skin reactions and vulval disorders. Rare complications of the medication include erythema of the eyes, abnormal eye sensation, syncope, tremor, vertigo, genital itching, painful intercourse and ovarian cyst rupture. It is the reports on liver injury in the recent time that have led to the temporary suspension of the use of UPA.29

Study design and Oversight

We conducted this randomized, parallel-group, double-blind, placebo-controlled, phase 3 trial from October 2020 through Feb 2020 Department of Obs and Gnae, LBKMCH, Saharsa. The study was approved by the independent ethics committee at each participating site and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines.

Table 1:- Baseline Characteristics of the Modified Intention-to-Treat Population.*

Characteristic	**Placebo (N = 48)**	**Ulipristal Acetate, 5 mg (N = 95)**
Age-yr	41.6±5.6	41.2±5.9
Body-mass index‡	24.6±4.4	25.9±4.6
PBAC score§		
median	**376**	**386**
Total fibroid volume at screening — cm3		
median	**61.5**	**100.7**
Hemoglobin — g/dl	9.55±1.18	9.32±1.50
Assessment of pain		
Short-Form McGill Pain		

Questionnaire‖		
median	8.5	6.5
Visual-analogue scale**		
median	16.0	14.0

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The pictorial blood-loss assessment chart (PBAC) is a validated method used to objectively estimate blood loss. Monthly scores range from 0 (amenorrhea) to more than 500, with higher numbers indicating more bleeding.
‖ Scores on the Short-Form McGill Pain Questionnaire range from 0 to 45, with higher scores indicating more severe pain.
** Scores on the visual-analogue scale range from 0 to 100, with higher scores indicating more severe pain.

study population Women 18 to 50 years of age were eligible if they met the following criteria: a score on the pictorial blood-loss assessment chart (PBAC, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding) higher than 100 during days 1 to 8 of menstruation; fibroid related anemia, defined as a hemoglobin level of 10.2 g per deciliter or lower without macrocytosis ; a myomatous uterus with a size equivalent to that of a uterus at 16 weeks or less of gestation; at least one fibroid that was 3 cm or more in diameter, but with no fibroid measuring more than 10 cm in diameter, as measured by ultrasonography; and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18 to 40.

We randomly assigned women with symptomatic fibroids, excessive uterine bleeding (a score of >100 on the pictorial blood-loss assessment chart [PBAC, an objective assessment of blood loss, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding]) and anemia (hemoglobin level of ≤10.2 g per deciliter) to receive treatment for up to 13 weeks with oral ulipristal acetate at a dose of 5 mg per day (95 women) or to receive placebo (48 women). All patients received iron supplementation. The coprimary efficacy end points were control of uterine bleeding (PBAC score of <75) and reduction of fibroid volume at week 13

The investigator assigned patients to a study group with the use of a Web-integrated interactive voice-response system. Study materials and medication packaging were identical for all three groups. Treatment was initiated during the first 4 days of menstruation. All patients received 80 mg of iron supplementation once daily during the active-treatment phase. In addition, iron could be prescribed during the screening and follow-up periods at the discretion of the investigator

Assessment of Uterine Bleeding
Menstrual bleeding was assessed with the use of the PBAC,30 a validated method used to objectively estimate blood loss. Monthly scores range from 0 (amenorrhea) to more than 500, with higher numbers indicating more bleeding. Patients were provided with standardized sanitary materials and recorded the numbers of tampons or pads they used and the extent of soiling with blood (see the Supplementary Appendix for a sample PBAC and an example of the calculation of the score). Menorrhagia was defined as a PBAC score of more than 100 during one menstrual period, which corresponds to a blood loss of more than 80 ml. A PBAC score of 400 corresponds to a blood loss of approximately 300 ml or the use of approximately 80 tampons or pads.30 At screening, patients were taught to use the PBAC and were asked to complete it daily throughout the treatment period up to week 13 and for 28 days preceding the post-treatment follow-up visits at weeks 26 and 38. The PBAC score for a 4-week period was calculated from the sum of daily PBAC results for 28 days.

End Points
The coprimary efficacy end points were the percentage of patients with a reduction in uterine bleeding at week 13, defined as a PBAC score (summed over the preceding 28-day period) of less than 75, and the change in total fibroid volume from screening to week 13, as assessed by magnetic resonance imaging (MRI) and read centrally by a radiologist who was unaware of the studygroup assignments. The total fibroid volume was the sum of the individual fibroid volumes.

Secondary end points included the bleeding pattern (consecutive 28-day PBAC scores); amenorrhea (PBAC 28-day score of ≤2 at weeks 9 and 13); reduction in uterine and fibroid volume (i.e., the percentages of women with at least a 25% reduction); changes in hemoglobin, hematocrit, and ferritin levels; pain, as measured with the use of the Short-Form McGill Pain Questionnaire31 (which includes a questionnaire on which scores rangefrom 0 to 45, with

higher scores indicating more severe pain, as well as a visual-analogue scale ranging from 0 to 100, with higher scores indicating more severe pain); The efficacy analyses were based on the 13-week measurements;

Statistical Analysis

Efficacy analyses were performed according to the intention-to-treat principle. We excluded one patient in the 5-mg ulipristal acetate group who was withdrawn before she received any study drug. the statistical tests were two-sided, with a 5% level of significance. Since the planned analyses involved comparisons 5mg of ulipristal acetate with placebo, a Bonferroni correction was used (all P values were doubled). No further adjustments for multiplicity have been made, since the efficacy outcome for each dose group was considered to be successful only if there were significant improvements over placebo in both coprimary efficacy end points. In general, missing values were imputed for the statistical analyses with the use of the last available post-baseline value up to the time point of interest.

The percentages of patients with a PBAC of less than 75 at week 13 were compared with the use of a Cochran–Mantel–Haenszel test (with adjustment for randomization strata), with confidence intervals calculated with the use of the Newcombe–Wilson score method (uncorrected).32 Additional binary end points were analyzed in a similar way. For the coprimary end point of the change in total fibroid volume, the data did not meet the assumptions of parametric tests and were analyzed with the use of the van Elteren extension to the Wilcoxonbrank-sum test with adjustment for randomization strata, with the Hodges–Lehmann estimator (and corresponding Moses confidence interval) used for the differences in medians.33The changes from baseline in PBAC scores and in pain assessments were analyzed in a similar way. Data on uterine volume were log-transformed and were evaluated with the use of an analysis of covariance; hemoglobin and hematocrit values were analyzed with the use of a repeated-measures analysis of covariance, with adjustment for the value at screening and for randomization strata in all analyses. The estimations of the sample size were based on the end point of change in fibroid volume, since more subjects were needed to show a significant treatment-related difference between the activetreatment groups and the placebo group for this end point than for the bleeding end point. Assuming a 10% dropout rate, we estimated that 143 patients would have to undergo randomization (95 in each ulipristal acetate group and 48 in the placebo group) for the study to have 90% power to show a significant between-group difference, assuming an average difference of −0.1 (approximately 20% change from baseline) in the change in log10 total fibroid volume between the ulipristal acetate groups and the placebo group and a between-patient standard deviation of 0.15.

Results:-

Primary Efficacy End Points

Menstrual bleeding was controlled in 91% of the women who received 5 mg of ulipristal acetate, as compared with only 19% of the women who received placebo (P<0.001 for the comparison of each ulipristal acetate group with the placebo group) (Table 2). There were statistically and clinically significant reductions in fibroid volumes in both ulipristal acetate groups as compared with the placebo group (Table 2

Secondary End Points

There were large reductions in bleeding (median changes in PBAC score of >300) in the patients who received either dose of ulipristal acetate, whereas there was little change in the patients who received placebo (P<0.001 for the comparison of each ulipristal acetate group with the placebo group at weeks 13). The majority of patients in the ulipristal acetate groups, but few patients in the placebo group, had amenorrhea after 4 weeks of receipt of the study drug (P<0.001 for the comparison of each ulipristal acetate group with the placebo group). The percentage of patients with a hemoglobin level higher than 12 g per deciliter and a hematocrit level higher than 36% increased over time in all groups. Hemoglobin and hematocrit levels were significantly higher in both ulipristal acetate groups than in the placebo group at all time points after the initiation of treatment A significantly greater percentage of patients in both ulipristal acetate groups than in the placebo group had a reduction in fibroid volume of at least 25% (P = 0.01) As compared with placebo. 5 mg of ulipristal acetate led to reductions in pain (especially moderate or severe pain), as measured with the use of the Short-Form McGill Pain Questionnaire

The rate of the occurrence of any adverse events did not differ significantly among the three groups. Headache and pain, discomfort, or tenderness in the breasts were the most common adverse events in the ulipristal acetate groups, but the events didnot occur significantly more frequently in these

groups than in the placebo group . The rate of hot flashes was low (<3%) in all groups.
Two serious adverse events occurred during thetreatment period: one event of a fibroid protruding through the cervix (in the placebo group) and one event of uterine hemorrhage (in the 5-mg ulipristal acetate group).

Table 2:- Key Efficacy End Points in the Modified Intention-to-Treat Population.*

End Point	**Placebo (N = 48)**	**Ulipristal Acetate, 5 mg (N = 95**	**Difference, 5 mg Ulipristal Acetate − Placebo (95% CI)†**	**P Value**
Primary end points at wk 13				
PBAC <75 — no./total no. (%)	9/48 (19)	86/94 (91)	73 (55 to 83)	<0.001
% Change from screening in total fibroid volume‡ median	3.0	−21.2	−22.6 (−36.1 to −8.2)	0.002
Secondary end points				
Amenorrhea, PBAC ≤2, at wk 9–12 — no./total no. (%)	3/48 (6)	69/94 (73)	67 (50 to 77)	<0.001
Hemoglobin — g/dl				
Baseline	9.55±1.18	9.32±1.50		
Week 13	12.61±1.30	13.50±1.32		
Change from baseline to wk 13	3.10±1.68	4.25±1.90	0.92 (0.39 to 1.44)	<0.001
Pain assessment with Short-Form McGill Pain Questionnaire				
Change from baseline to wk 13				
median	-2.5	-5.0	−2.0 (−4.0 to 0.0)	0.10

Discussion:-

In this randomized, double-blind, placebo-controlled trial, oral ulipristal acetate at a dose of 5 mg per day was effective in controlling excessive bleeding and shrinking fibroids in patients who had severe bleeding and associated anemia at baseline. Treatment with ulipristal acetate, as compared with placebo, also resulted in clinically significant increases in hemoglobin and hematocrit levels and reductions in self-reported pain and discomfort due to fibroids. Current medical therapies for fibroids have limitations.4,34 Although treatment with a GnRH agonist before surgery results in a lower frequency of midline incisions, a greater likelihood of vaginal, as compared with abdominal, hysterectomy, and a reduction in intraoperative blood loss, GnRH agonists cause side effects such as hot flashes and atrophic vaginitis that may reduce adherence to therapy.12 Pilot and phase 2 trials have previously suggested a benefit of selective progesterone-receptor modulators for the treatment of fibroids.23-26 This phase 3 trial involving women with fibroid-related anemia confirms and extends the findings of prior, smaller studies.24,25 Heavy menstrual bleeding is a major cause of doctor visits and lost work days.6 In this study, bleeding was controlled within 8 days after the beginning of the treatment period in the majority of patients in the ulipristal acetate groups but in few patients in the placebo group. Anemia was corrected from week 5 on in significantly more patients in the ulipristal acetate groups than in the placebo group. With iron supplementation, anemia was eventually corrected in most patients in the placebo group, despite ongoing bleeding. However, iron supplements may have adverse events, and

absorption is variable.35 In our study, the frequency of hot flashes was similar in the ulipristal acetate and placebo groups. Previous studies involving women treated with ulipristal acetate for up to 6 months identified cases of progesterone-receptor modulator–associated endometrial changes, including cystic glandular alterations,24,27 but reversibility was not investigated. A limitation of this study is that the duration of treatment was restricted to 13 weeks. More data are needed to inform the benefits and risks of long-term treatment with ulipristal acetate In conclusion, treatment with ulipristal acetate (at a dose of 5 mg) for 13 weeks was effective in controlling bleeding, decreasing fibroid volume, and reducing discomfort in women with menorrhagia and anemia.

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