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A Randomized controlled trial evaluating role of Ulipristal acetate versus leuprolide acetate in management of fibroid- Redefining role of each!

Dr. Surendra and Dr. Vinu Choudhary

Abstract
Introduction: Ulipristal acetate is a selective progesterone-receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antiglucocorticoid activity. 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 anemia.
Methodology: This was a randomized controlled trial study conducted at a tertiary care hospital situated in an urban area. A total number of 30 patients with symptomatic fibroids were enrolled in this study. The patients were divided into two groups (Group A and B) of 15 patients each according to whether they received either Ulipristal acetate 5 mg OD orally daily or leuprolide injection 3.75 mg once in a month.
The primary outcome was evaluated in terms of change in size of fibroid, reduction in pain, resolution of menorrhagia and improvement in quality of life.
Result: A total number of 30 patients with symptomatic fibroids were enrolled in this study. Results were tabulated and analyzed using SPSS 16.0 version software. Microsoft word and excel were used for generating charts and graphs. P value <0.05 is considered statistically significant.
Demographic profile of both the groups were comparable no statistically significant difference was noted. Symptomatic relief provided by both the drugs are comparable, ulipristal had an edge over leuprolide when fibroid was > 5 cm in size although the difference was not statistically significant. Adverse effects were more common with leuprolide when compared with ulipristal (p value>0.05). Time taken to control the symptoms is less with ulipristal though not statistically significant.
Conclusion: We conclude from this study that both these drugs can be used for treatment of symptomatic fibroids. Ulipristal acetate should be preferred over leuprolide depot when the fibroid size is found to be more than 5 cm.
Key message: Further original clinical studies of large sample size to identify the optimal indications for UPA in patients with symptomatic fibroid.

Keywords: ulipristal, leuprolide, symptomatic fibroid, menorrhagia, pain, quality of life

Introduction
Uterine leiomyomas, or fibroids, are the most common benign uterine tumors in women of reproductive age [1, 2]. In addition to anemia caused by heavy bleeding, fibroids can cause pelvic pain, pressure, dysmenorrhea, reduced quality of life, and infertility. Terine leiomyomas, or fibroids, are benign, hormone-sensitive, smooth-muscle tumors that occur in 20 to 40% [3, 4] of women of reproductive age. The most common symptoms are menorrhagia and iron-deficiency anemia, which may lead to chronic fatigue that may not be adequately controlled with iron supplementation alone. Other symptoms include pelvic pain, dysmenorrhea, and pressure effects, which may adversely affect quality of life and fertility [5, 6]. The exact etiology of fibroids is debatable but many factors are reported to have some role in the pathogenesis of fibroids including genetic, hormonal and biological factors. The risk factors for developing fibroids include obesity, nulliparity, younger age at menarche and African race.
Many patients require intervention, and the choice of treatment is guided by the patient's age and desire to preserve fertility and avoid hysterectomy. Fibroids are the most common indication for hysterectomy. Other treatments include myomectomy, hysteroscopic removal, uterine-artery embolization, and various other interventions performed under radiologic guidance [7, 8].
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 anemia; 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, and they may promote proliferation of fibroids. 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.

Current management strategies [9, 10] consist mainly of surgical or radiologic interventions; options for medical therapy are limited. The use of oral progestin has not been extensively investigated, but small studies report breakthrough bleeding and possible promotion of myoma growth. Ulipristal acetate is a selective progesterone-receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antiglucocorticoid activity. In addition, SPRMs have pharmacodynamic effects on the endometrium, including antiproliferative effects that may contribute to the induction of amenorrhea. SPRMs are a new class of PR ligands that display tissue-selective effects on target cells. UPA is an orally active synthetic SPRM that is characterized by a tissue-specific progesterone antagonist effect [11]. UPA reduces the proliferation of leiomyoma cells and induces apoptosis by increasing the expression of cleaved caspase-3 and decreasing the expression of Bcl-2. Conversely, UPA downregulates the expression of angiogenic growth factors and their receptors [12]. Thus, it inhibits neovascularization, cell proliferation, and survival in leiomyoma cells, but not in normal myometrial cells. UPA also has a central action on the hypothalamic–pituitary–ovarian axis, and it inhibits or delays ovulation. In small placebo-controlled trials, ulipristal acetate reduced fibroid and uterine sizes in women with symptomatic fibroids.

Methodology

This was a randomized controlled trial study conducted at a tertiary care hospital situated in an urban area. A total number of 30 patients with symptomatic fibroids were enrolled in this study. The patients were divided into two groups (Group A and B) of 15 patients each according to whether they received either Ulipristal acetate 5 mg OD orally daily or leuprolide injection 3.75 mg once in a month.

We enrolled premenopausal women between the ages of 18 and 50 years who had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18 to 40, heavy uterine bleeding caused by fibroids, at least one myoma measuring 3 cm or more in diameter (but no myoma measuring >10 cm), and a uterine size equivalent to that of a pregnancy of no more than 16 weeks of gestation; all patients were eligible for surgery. Detailed history and demographic profile was noted in all the cases. Menstrual blood loss was assessed by taking into account number of pads soaked, degree of soakage and passage of clots. Any history of dysmenorrhea, dyspareunia or menorrhagia was noted. A complete general and systemic examination followed by gynecological examination was done. Patients were followed up for 3 months and the parameters like change in fibroid size, reduction in pain, resolution of menorrhagia and improvement in quality of life was compared between these 2 groups.

Inclusion criteria

- Females diagnosed to be having uterine fibroids in reproductive age group
- Patients having symptoms like menorrhagia, dysmenorrhea, or any symptoms related to fibroids
- Single fibroid measuring >= 3 cm.
- Patients having consented to be part of this study.

Exclusion criteria

- Pregnant women
- Those who giving consent
- Myoma >10 cm
- Uterine size >16 wks.
- Renal or hepatic dysfunction
- Patients having adenomyosis, endometrial hyperplasia or genital tract infections

The primary outcome was evaluated in terms of change in size of fibroid, reduction in pain, resolution of menorrhagia and improvement in quality of life.

Result

A total number of 30 patients with symptomatic fibroids were enrolled in this study. Results were tabulated and analyzed using SPSS 16.0 version software. Microsoft word and excel were used for generating charts and graphs. P value <0.05 is considered statistically significant.

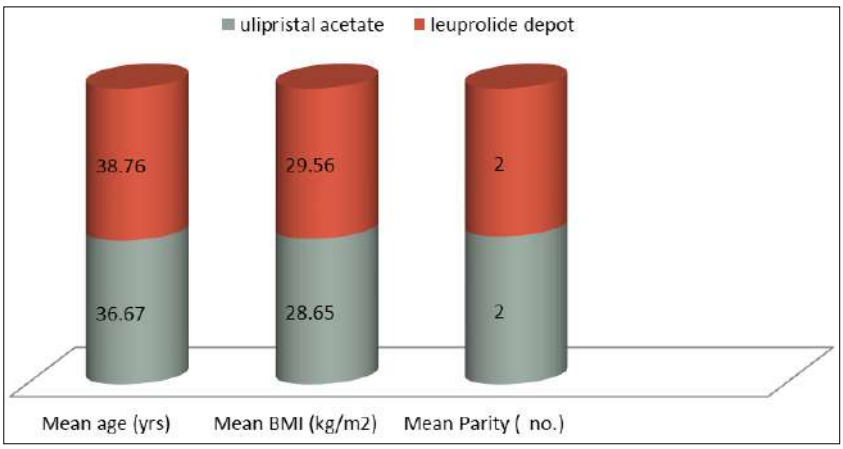

Fig 1: Baseline demographic profile in both groups.

P value >0.05

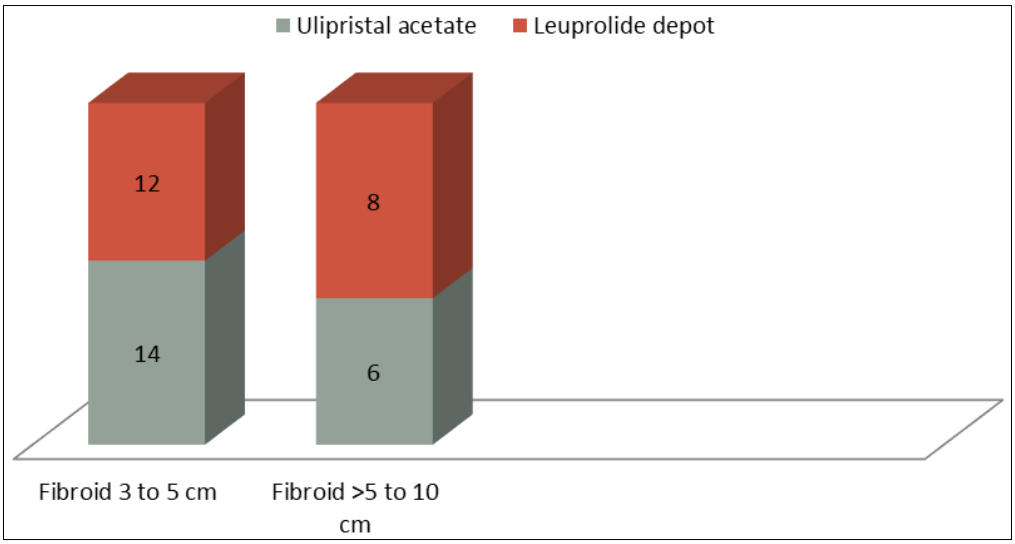

Fig 2: Fibroid size in both groups.

P value >0.05.

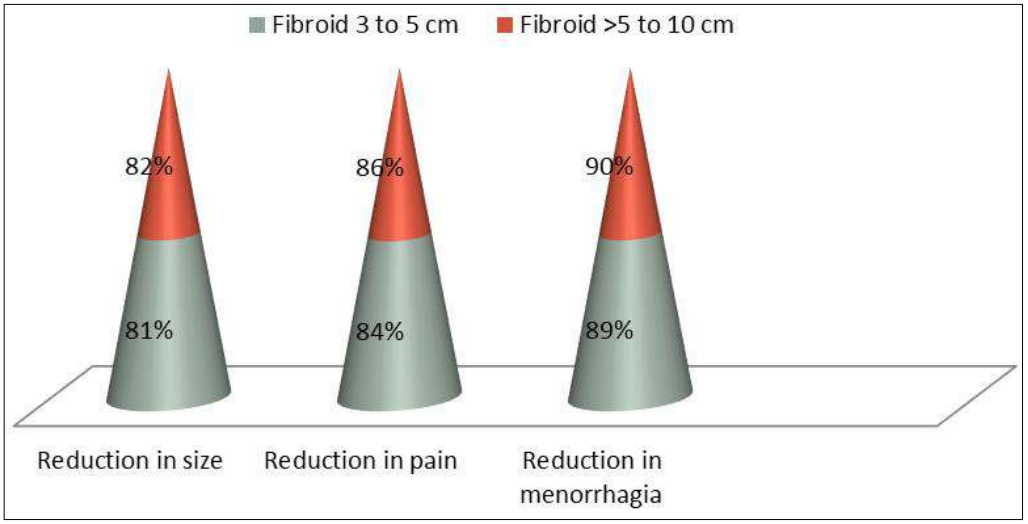

Fig 3: Reduction in signs & symptoms in ulipristal acetate group (Gp. A)

P value >0.05.

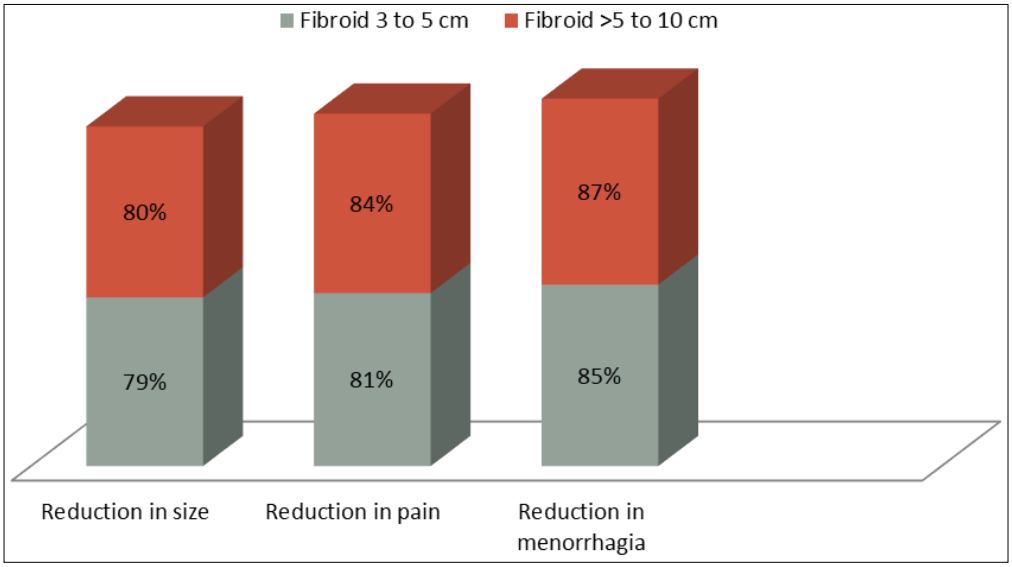

Fig 4: Reduction in size & symptoms in leuprolide depot group (Gp. B)

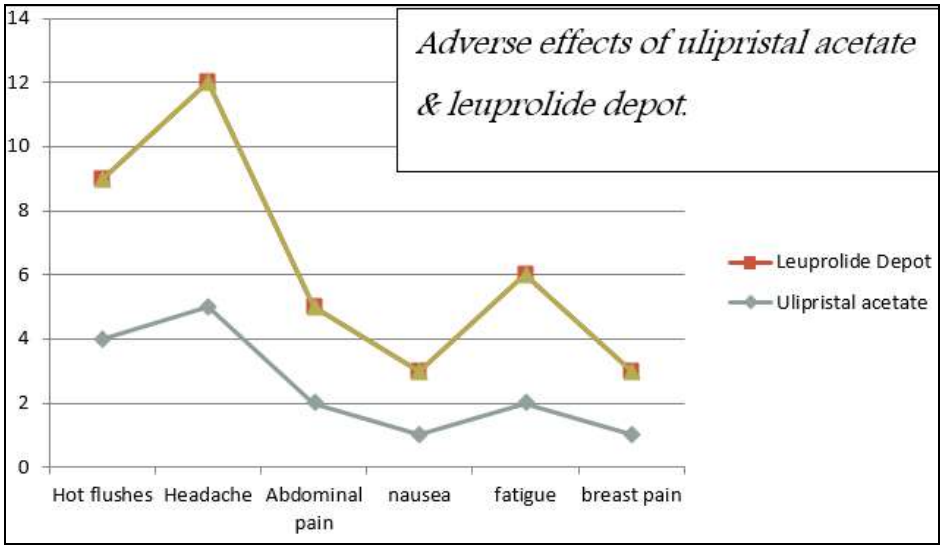

Fig 5: Adverse effects of uliprital acetate & leuprolide acetate.

P value>0.05.

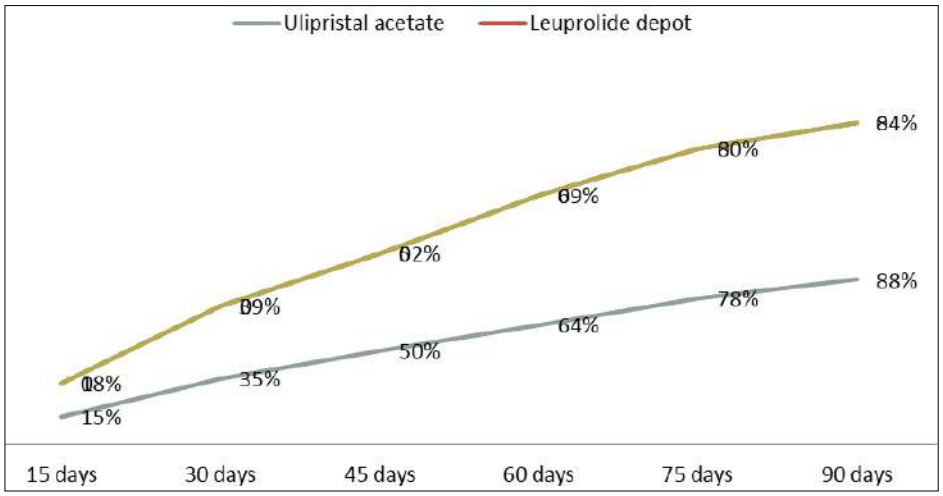

Fig 6: Time taken for control of symptoms

P value >0.05.

Discussion

Selective Progesterone receptor modulators (SPRMs) like Ulipristal Acetate & leuprolide depot 3.75 mg once a month have been used for the treatment of dysfunctional uterine bleeding and uterine myomas because of their antiproliferative effects on endometrium and myometrium. In 1993 Murphy *et al* first described use of mifepristone for the treatment of uterine fibroid. They showed uterine fibroids to be steroid hormone dependent tumors possessing Estrogen and progesterone receptors (ER and PR) [12, 14]. They proposed that antiprogesterone reduce the size of uterine fibroids either by blocking the effect of progesterone or interference of Estrogen action on fibroids. The authors examined the effects of daily administration of ulipristal acetate 5 mg for a period of 3 months in 10 patients with uterine fibroids. Baseline ultrasound examinations were obtained and repeated monthly during treatment as a measure of fibroid size. The authors found that fibroid volume (Mean±SE) decreased 21.9±4.8% after 4 weeks, 39.5±6.6%[14].

In the present study demographic profile of both the groups were comparable no statistically significant difference was noted. Symptomatic relief provided by both the drugs are comparable, ulipristal had an edge over leuprolide when fibroid was > 5 cm in size although the difference was not statistically significant. Adverse effects were more common with leuprolide when compared with ulipristal (p value>0.05). Time taken to control the symptoms is less with ulipristal though not statistically significant. These all findings were supported by Donnez *et al*. [14, 15] Very less studies are available comparing the role of ulipristal & leuprolide. More studies are required to precisely define the role of each in management of fibroid uterus.

Similarly, the utility of Ulipristal acetate has been tested in many randomized controlled trials. The first large randomized controlled trial for use of Ulipristal acetate in medical management of fibroids [15] (PEARL I) compared it with placebo in uterine fibroids. The study found that use of Ulipristal acetate was associated with significant reduction in menorrhagia and fond that bleeding was controlled in 91%, 92%, and 19% of the women receiving UPA (5 mg), UPA (10 mg), and placebo, respectively. This staggering difference in control of bleeding made many researches take up the studies using Ulipristal acetate for medical management of uterine fibroids. PEARL II study was another randomized controlled trial comparing Ulipristal acetate with GnRH analog in the medical management of uterine fibroids. The study [15] found that menorrhagia was controlled in 90%, 98%, and 89% of the women receiving Ulipristal acetate (5mg), Ulipristal acetate (10mg) and GnRH analogue, respectively. The authors concluded that Ulipristal

acetate use was associated with a quicker control of menorrhagia as compared with GnRH analogues. The reduction of fibroid size, reduction in pain and decreased incidence of menorrhagia was associated with improved quality of life in patients receiving Ulipristal acetate. The findings were similar to the present study we found that administration of Ulipristal acetate 10 mg daily was associated with reduction in fibroid size in 80%. Various other studies have shown the effectiveness of Ulipristal acetate in decreasing menorrhagia and improving the quality of life of patients with uterine fibroids. In a recent study Kalampokas T *et al*. [13] found that treatment of patients with Ulipristal acetate was associated with improved quality of life parameters and reduction in fibroid size. They concluded that Short-term use of Ulipristal acetate is effective and safe method of treating uterine fibroids. All these findings were similar to findings of our study.

Conclusion

The role of ulipristal will be determined by each patient's problems. While surgery will remove fibroids, this may not be appropriate for women planning a future pregnancy. It is possible that ulipristal could reduce the size of the fibroids to enable less invasive surgery. For women who do not want surgery more research will be needed on repeated courses of ulipristal.

We conclude from this study that both these drugs can be used for treatment of symptomatic fibroids. Ulipristal acetate should be preferred over leuprolide depot when the fibroid size is found to be more than 5 cm.

Key message

UPA may be a good option for women seeking pregnancy, for women who wish to avoid surgery, or before surgery to reduce the invasiveness of the operation. The heterogeneity of these possible indications will require further original clinical studies of large sample size to identify the optimal indications for UPA in patients with symptomatic fibroid.

References

1. Kalampokas T, Kamath M, Boutas I. Ulipristal acetate for uterine fibroids: a systematic review and meta-analysis. Gynecol Endocrinol. 2016; 32(2):91-6.
2. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. Int J Women's Health. 2014; 6:95-114.
3. Purohit P, Vigneswaran K. Fibroids and Infertility. Current Obstet Gynecol Reports. 2016; 5:81-8.
4. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers. 2016; 2:16043.
5. Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of uterine myomas: a review. Int J Fertility Sterility. 2016; 9(4):424-35.
6. Sue W, Sarah SB. Radiological appearances of uterine fibroids. Indian J Radiol Imaging. 2009; 19(3):222-31.
7. Levens ED, Wesley R, Premkumar A, Blocker W, Nieman LK. Magnetic resonance imaging and transvaginal ultrasound for determining fibroid burden: implications for clinical research. Am J Obstet Gynecol. 2009; 200(5):537.
8. Aluwee SAZBS, Kato H, Zhou X, Hara T, Fujita H, Kanematsu M *et al*. Magnetic resonance imaging of uterine fibroids: a preliminary investigation into the usefulness of 3D-rendered images for surgical planning. Springer Plus. 2015; 4:384.
9. Murji A, Whitaker L, Chow TL, Sobel ML. Selective progesterone receptor modulators (SPRMs) for uterine fibroids. Cochrane Database Syst Rev. 2017; 4:CD010770.
10. Arendas K, Leyland NA. Use of ulipristal acetate for the management of fibroid-related acute abnormal uterine bleeding. J Obstet Gynaecol Can. 2016; 38(1):80-3.
11. Woźniak S, Szkodziak P, Czuczwar P. The effect of ulipristal acetate treatment on symptomatic uterine fibroids within 12-months follow-up. Przegląd Menopauzalny Menopause Rev. 2014; 13(1):18-21.
12. Bourdet TA, Luton D, Koskas M. Clinical utility of ulipristal acetate for the treatment of uterine fibroids: current evidence. Int J Women's Health. 2015; 7:321- 330.
13. Kalampokas T, Kamath M, Boutas I. Ulipristal acetate for uterine fibroids: a systematic review and meta-analysis. Gynecol Endocrinol. 2016; 32(2):91-6.
14. Jacques Donnez, Guillaume Courtoy E, Olivier Donnez, Marie-Madeleine Dolmans. Ulipristal acetate for the management of large uterine fibroids associated with heavy bleeding: a review. Reproductive BioMedicine Online. 2018; 37(2):216-223.
15. Donnez *et al*. Ulipristal acetate versus leuprolide acetate for uterine fibroids N Engl J Med. 2012; 366:421-432.