|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article Volume 3, Issue 9; September: 2019; Page No. 200-205

STUDY TO COMPARE THE EFFICACY AND SAFETY OF ULIPRISTAL ACETATE AND MIFEPRISTONE AS MEDICAL TREATMENT OF UTERINE FIBROID.

[1]Dr. Sushmita Prasad, [2*]Dr. Subhashree Sethi
[1] MS. Obstetrics and Gynecology, Patna Medical College and Hospital, Patna.
[2*] MS. Obstetrics and Gynecology, Patna Medical College and Hospital, Patna.

Article Info: Received 02 September 2019; Accepted 24 September. 2019
DOI: https://doi.org/10.32553/ijmbs.v3i9.569
Corresponding author: Dr. Subhashree Sethi
Conflict of interest: No conflict of interest.

Abstract
Uterine fibroids are one of the most common benign uterine tumors seen in females of reproductive age group. They either may be completely asymptomatic (diagnosed incidentally while doing ultrasound for some other reason) or may present as menorrhagia, lower abdominal or back pain, pelvic mass, obstructive uropathy, anemia secondary to blood loss and infertility. The management of uterine fibroids depends upon factors like possibility of pregnancy in future, whether preservation of uterus is desirable, severity and characteristics of symptoms. Various treatment options include observation and follow up, medical management (Mifepristone or Ulipristal acetate), uterine fibroid embolisation and hysterectomy. This study was done to know the effect of ulipristal acetate and mifepristone on Menstrual blood Loss, Dysmenorrhea, Uterine size & fibroid size. This was a comparative study done in 160 patients attending outpatient department of Obstetrics and Gynaecology of Patna Medical College and Hospital (PMCH). Treatment of symptomatic fibroids by Mifepristone as well as Ulipristal acetate was associated with reduction in fibroid size, reduced blood loss and decreased pain. We conclude from this study that both these drugs can be used for treatment of symptomatic fibroids

Keywords: Uterine Fibroid, Ulipristal Acetate, Mifepristone

INTRODUCTION

A Uterine fibroid is the most common type of benign tumor of uterus and also the most common pelvic tumor in women. Uterine fibroid (also called uterine leiomyoma, myoma, fibromyoma, fibroleiomyoma & fibroma) is non-cancerous benign tumour that originates from the smooth muscle layer and the accompanying connective tissue of uterus. It occurs one in every four or five women of reproductive age, typically reported in 20-40% of reproductive age group women. Approximately one half of all women 35-49 years of age have fibroid which are estimated to be responsible for 1.2 million hospitalisation per year & >1 million hysterectomy. Incidence of this pathology is up to 25%,appearing in about 35% of women in menopausal age group. Uterine fibroids are one of the most common benign uterine tumors seen in females of reproductive age group. [1] In general, the prevalence of symptomatic fibroid peaks in the perimenopausal years and declines after menopause. Their prevalence is high upto 40% of women aged around 50 years, although there are well documented racial differences in prevalence rates. As per a study conducted by National institute of health in India about 25 % of women of the reproductive years have symptomatic fibroids. They either may be completely asymptomatic (diagnosed incidentally while doing ultrasound for some other reason) or may present as menorrhagia, lower abdominal or back pain, pelvic mass, obstructive uropathy, anemia secondary to blood loss and infertility.[2] The percentage of patients having symptomatic uterine fibroids is reported to range from 25-30%.[3]As per a country or region extrapolated prevalence population estimated to have uterine fibroid in india is 53,253530 in a total population of 1,065,070,6072 and also it was observed that thousands of the fibroid uterus progresses into malignant lesion at later stage . 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. [4] The diagnosis of uterine fibroids is usually done by ultrasound

examination which usually shows a welldefined hypoechoic lesion within myometrium having a characteristic peripheral vascularity on Doppler examination. [5]UThe sensitivity of transvaginal ultrasounds more that transabdominal ultrasound in the diagnosis of small fibroids. [6]Uterine fibroids are responsive (increase their growth or size and symptoms) to hormonal factors including estrogen ,progesterone and insulin like growth factor I (IGF-I). IGF-I stimulates uterine myoma cell growth, enhancing proliferation, and inhibiting apoptosis, while progesterone (alone or in combination of estradiol) down-regulates IGF-I mRNA and protein expression in fibroid cells. There appears to be genetic variation in leiomyoma prevalence as African-American women in US have a 3 fold higher risk of developing leiomyoma. The incidence of malignancy in fibroids is less than 0.1%. Significant and often disabling symptoms including heavy menstrual bleeding and painful menstruation, urinary frequency and urgency, abdominal & pelvic pain, dysmenorrhea, in some case infertility and spontaneous abortion if pregnancy occurs. Heavy menstrual bleeding (HMB) is the most common symptom associated with fibroid. Cramping pain, ischaemic acute pain, pelvic pressure, discomfort during sexual intercourse and urinary symptoms are due to degeneration caused by insufficient blood supply in rapidly growing fibroids. If the women have heavy menstrual bleeding, the NICE recommends consideration of medical treatment when fibroid are <3 cm in diameter and causing no distortion of uterine cavity. The complications associated with uterine fibroids may include severe anemia requiring intervention in the form of transfusions, hyaline or red degeneration, urinary retention, hydronephrosis secondary to obstructive uropathy and rarely sarcomatous changes.[7,8] Uterine fibroid can be managed either by surgery or by medical therapy. Medical therapy intends to reduce or eliminate the symptoms related to leiomyoma by decreasing the size of myoma or the amount of bleeding. Mifepristone and selective progesterone receptor modulators (SPRMs) have suggested that these agents may be useful in treating fibroids .Both Ulipristal acetate (UPA) and Mifepristone are SPRMs that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation. Mifepristone has been in use since 2002 while UPA has recently been used for fibroids .Studies of cultured fibroid cells have shown antiproliferative and antifibrotic and pro apoptotic effects of UPA on these cells but not on normal myometrial cells. UPA has high affinity for PR-A and B receptor and less affinity for glucocorticoid receptors as compared to Mifepristone .At the same time it doesnot suppress estradiol E2 to nonphysiologic level. So this study has been conducted in PMCH to compare efficacy and side effect of mifepristone and UPA as an alternative to surgical management of symptomatic uterine fibroids.

Material and Methods:

This was a comparative study done in 160 patients attending outpatient department of Obstetrics and Gynaecology of Patna Medical College and Hospital (PMCH). The study period was September 2016 to September 2018.

Selection of cases:

Patients were divided into two groups

Group I(ulipristal acetate) – Comprised of 80 patients to whom 5mg of UPA was given orally daily for 3 months started within 4 days after start of menstruation then stop for one full menstrual cycle and then recommenced within 4 days of second menstruation following 1st treatment course completion. Same dose was repeated for further 2 courses(total 3 courses)

Group II(mifepristone): Comprised of 80 patients to whom 25 mg mifepristone was given daily for 9 months starting from D1 toD7 of menstrual cycle.

INCLUSION CRITERIA:

1) Female from 18 yrs to premenopause(approx 50yrs)

2) Having at least symptoms of menorrhagia, or pelvic pain or pressure symptom and fibroid of size < or = 3cm and maximum 4 in number.

3) Having a total uterine volume less than or equal to 160cc by ultrasound and at least 1 fibroid is ≥2.5cm in size.

4) Having good general health.

5) Willing & able to give informed consent.

Criteria for exclusion:

1) Pregnant women with fibroid.

2) Big myoma size

3) Presence of conditions other than fibroid contributing to pain or bleeding.

4) Presence of adenexal mass or tenderness

5) Presence of any contraindication to mifepristone including –

- Adrenal insufficiency
- Sickle cell disease
- Active liver disease
- Renal disease (Sr. creatinine - >1.5 mg/dl)

Informed consent was obtained from all the patients before enrolling them in to the study. Detail history and demographic profile was noted in all the cases. The criteria of selection of patients were on the basis of detailed history and thorough clinical examination. The patients were interrogated and their findings were recorded on the predesigned proforma in addition to her complains. Detailed obstetric history was taken in terms of parity and infertility. Demographic and baseline clinical profile including details of menstrual cycle ,symptoms and their severity was noted. According to WHO criteria, Hb less than 12 gm|dl was taken as anemia .Menstrual blood loss was assessed by PBAC score which is semiquantitative assessment that takes in to the account the number of pads soaked,degree of soakage ,passage of clots. This study was done to know the effect of ulipristal acetate and mifepristone on Menstrual blood Loss, Dysmenorrhea, Uterine size & fibroid size, Tolerability of both drugs. Investigations done to know the outcome were Baseline Haemoglobin, TLC, DLC, SGPT, Blood urea, Sr. Creatinine, Blood sugar and serum electrolyte, then repeated at 2 month interval. Ultrasonograms for uterine volume and fibroid volume .Endometrial biopsy were taken 1st at time of registration as baseline then repeated after 3 months & after 6months.

Results:

Table 1: Age group distribution.

Age Group				
Age Group	**Group – I (Mifepristone)**	**%**	**Group - II (UPA)**	**%**
20-29	32	40%	36	45%
30-39	20	25%	20	25%
40-49	28	35%	24	30%
Total	80	100%	80	100%

Mean age in group I was 39.20 yrs & in Group II was 39.10 yrs.Mean parity in group I was 2.34 & in group II was 2.7.

Table 2: Menstruation blood loss - Prevalence of Baseline Menstrual Symptoms

Prevalence of Baseline Menstrual Symptoms						
Symptoms		**Group - I (Mifepristone)**		**Group - II (UPA)**		**P-Value**
		N	**%**	**N**	**%**	
Menstruation	Heavy	44	55%	48	60%	>0.05
	Moderate	36	45%	32	40%	>0.05
	Light	0	0	0	0	0
	Spotting	0	0	0	0	0
	None	0	0	0	0	0

Table 3: Prevalence of Menstrual Symptoms at 9-Months: Menstruation

Prevalence of Menstrual Symptoms at 9-Months					
Symptoms		**Group - I (Mifepristone)**		**Group - II (UPA)**	
		n	**%**	**N**	**%**
Menstruation	Heavy	0	0	0	0
	Moderate	0	0	0	0
	Light	0	0	0	0
	Spotting	6	8.82%	5	7.15%
	None	62	91.1%	65	92.8%

In group 1 and 2 heavy menstruation was present (55% and 60%) before startindg treatment. After 9 months it reduced to 8.82% and 7.15% .

Table 4: Prevalence of Baseline Menstrual Symptoms: Dysmenorrhea

Prevalence of Baseline Menstrual Symptoms						
Symptoms		**Group - I (Mifepristone)**		**Group - II (UPA)**		**P-Value**
		n	**%**	**n**	**%**	
Dysmenorrhea	Severe	8	10%	4	5%	<0.001
	Moderate	16	20%	6	7.5%	>0.05
	Mild	24	30%	32	40%	<0.01
	None	32	40%	38	47.5%	-

Table 5: Prevalence of Menstrual Symptoms at 9-Months: Dysmenorrhea

Prevalence of Menstrual Symptoms at 9-Months					
Symptoms		**Group - I (Mifepristone)**		**Group - II (UPA)**	
		n	**%**	**n**	**%**
Dysmenorrhea	Severe	0	0	0	0
	Moderate	0	0	0	0
	Mild	6	8.8%	10	14.28%
	None	62	91.17%	60	85.71%

At baseline mild to moderate dysmenorrhoea was present in 40% of study group 1 and38% of group 2. After 9 months only 8.8% and 14.28% had mild dysmenorrhoea.

Table 6: Uterine Volume (Cc)

Uterine Volume (cc)							
Duration	Group - I (UPA)			Group - II (Mifepristone)			P-Value
	Mean (cc)	SD	% of Change to Baseline	Mean (cc)	SD	% of Change to Baseline	
Baseline	143.75	18.82	-	121.25	17.83	-	>0.05
3-Months	133.75	24.72	-6.95	113.19	25.45	-6.64	<0.001
6-Months	124.73	21.63	-13.23	106.80	23.41	-11.91	<0.001
9-Months	111.42	16.80	-22.49	102.50	18.86	-15.46	<0.001

At Baseline mean uterine volume in group I and II were 143.75 cc & 121.25cc, respectively and difference between them was non significant. While at 9 month mean uterine volume in Group I & Group II were 111.42 cc & 102.5cc respectably. This difference was found statistically significant.

Table 7: Fibroid Volume (Cc)

Fibroid Volume (cc)							
Duration	Group - I (UPA)			Group - II (Mifepristone)			P-Value
	Mean (cc)	SD	% of Change to Baseline	Mean (cc)	SD	% of Change to Baseline	
Baseline	37.125	14.64	-	36.62	13.91	-	>0.05
3-Months	30.00	13.95	-19.19	30.83	13.64	-15.81	<0.001
6-Months	29.05	13.80	-21.75	29.11	13.10	-20.50	<0.001
9-Months	21.71	13.21	-41.52	25.64	12.41	-29.98	<0.001

At baseline mean fibroid volume in group I and group II were 37.125cc & 36.62 cc. respectively & difference between them was non-significant. While at 9 month mean fibroid volume in Group I & II were 21.71 cc & 25.64 cc respectively, which was found to be statistically significant.

Table 8: Hemoglobin Level

Hemoglobin Level							
Duration	Group - I (UPA)			Group - II (Mifepristone)			P-Value
	Mean (gm/dl)	SD	% of Change to Baseline	Mean (gm/dl)	SD	% of Change to Baseline	
Baseline	10.00	1.18	-	9.60	1.14	-	<0.05
3-Months	11.00	1.06	+4.80	10.00	1.04	+4.17	<0.05
6-Months	11.60	1.00	+13.20	10.80	0.90	+12.50	<0.05
9-Months	12.50	0.86	+24.40	11.83	0.67	+23.13	<0.05

Baseline mean haemoglobin in group I & II were 10.0 g/dl & 9.6g/dl respectively. But after 9 months, mean haemoglobin in group I & group II were 12.50 g/dl and 11.83 g/dl respectively. This difference was found to be statistically not significant.

Discussion:

Fibroids are the most common tumours of the uterus and the female pelvis. They occur in upto 35% of women aged more than 35 years and account for up to 40% of all hysterectomies. During the past century, hysterectomy and myomectomy have been the main treatment for women with large or symptomatic fibroid. The availability of a safe and effective nonsurgical treatment of symptomatic fibroid would be of considerable clinical and public health importance. Medical therapy with nonsteroidal anti-inflammatory drugs, hormonal therapy with OC pills did not cause significant changes in symptoms following treatment for even a year.

Recent studies have shown that mifepristone and ulipristal acetate treatment reduced the prevalence and severity of dysmenorrhoea, menorrhagia, and pelvic pressure and also reduced the size of fibroid. The first study demonstrating the decrease in fibroid volume in response to progesterone antagonist was conducted by Murphy et al[9]. Several other clinical trials using mifepristone in doses of 5-50 mg were conducted for varying periods between 3 to 12 months. In 1980, Wilson EA, Yang F, Rees ED found a significantly higher concentration of estrogen receptors in Leimyomata than myometrium[10]. In 1993, According Bradon DD, Bethea CL, Strawn EY et al Progesterone receptor RNA is overexpressed in uterine leiomyoma, compared to normal adjacent myometrium, suggesting that amplified progesterone mediated signal is instrumental in the abnormal growth of there tumours[11]. In 2000, Rein MS provided further biochemical, hitological and clinical evidence that progesterone has a critical role in leiomyoma growth[12]. Recently mifpristone a progesterone receptor modulator with primarily antgonistic properties has been shown to decrease leiomyoma size. Mifepristone (RU 486) is a synthetic steroid with antiprogesterone and antiglucocorticoid activities activity. It was first synthesized in France by Baulieu in 1980[13] from the precursor norethindrone by French company Roussel Uclaf. It was the 38486th compound synthsised by Roussel Uclaf company ,so it was named in short as- RU486. Mifepristone is a 19 norsteroid that blocks the action of female hormone progesterone. Mifepristone in low daily doses has significant effects on the endometrium. Earliest study was done in 1993 by Murphy A, Kettel L, Moralis A, et al using 50 mg of mifepristone for 3 months. They found 49% reduction in leiomyoma volume. In 1994, Reinsh RC, Murphy AA, Morales AJ, Yen SS studied, the effect of 25mg mifepristone on fibroid for 3 month & found 32% reduction in fibroid volume with no incidence of hot flushes. In 2008, Steve H. Eisinger, Julietta Fiscella, Thomas Bonfiglio et al studied the effects of 2.5 mg mifepristone in fibroid & found significant improvement in symptoms in 6 months but uterine volume decreased by only 11%. Mifepristone offers promise for three clinical uses: First, mifepristone may be a viable alternative to GnRH analogues for use in the preoperative period. It appears to yield comparable reductions in leiomyoma symptoms and size and can be orally administered. It has the added advantage of not producing side effects such as hot flushes and osteoporosis. Due to reduction in fibroid size and amenorrhea, blood transfusion and its hazards can be avoided prior to or during surgery. It also improves surgical approach; an abdominal hysterectomy can be converted to vaginal hysterectomy and, a longitudinal incision can be converted to a transverse incision. Second, if the safety of long-term, low dose mifepristone is established, perimenopausal women with large, symptomatic fibroids typically regress. A major saving in cost and morbidity may be possible in view of the large number of hysterectomies done for fibroid in perimenopausal women. The third possible application occurs in younger age group with large leiomyoma who wish to retain their fertility. They may also benefit from long term low dose mifepristone, until they wish to attempt conception as the regrowth of fibroid after cessation of therapy takes longer duration than GnRH agonist.

Conclusion:

Of the population of more than 1 billion in India, about 50% are female, and 45% of these are in reproductive age group. The problem of utrine fibroid affects nearly 35% of this age group and unfortunately many of them suffer from for long periods before they obtain surgical treatment, if at all. An effective and inexpensive medical management for this major public health problem would be a great boon. The cost of treatment is a major factor in a developing country like India and women would often prefer medical management to surgery. The added risk of preoperative transfusion, anesthesia and surgery increase the morbidity and mortality. Hence Mifepristone could be a good alternative to surgery and preferable to other medical treatments for fibroids.

References:

1. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. Int J Women's Health. 2014;6:95-114.
2. Purohit P, Vigneswaran K. Fibroids and Infertility. Current Obstet Gynecol Reports. 2016;5:81-8.
3. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers. 2016;2:16043.
4. Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of uterine myomas: a review. Int J Fertility Sterility. 2016;9(4):424-35.
5. Sue W, Sarah SB. Radiological appearances of uterine fibroids. Indian J Radiol Imaging. 2009;19(3):222-31.
6. 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.
7. Purslow CE. Fibroid uterus with red degeneration and with early gestation. Proceedings of the Royal Society of Medicine. Obstet Gynecol Sect. 1914;7:300.
8. Al Ansari AA, Al Hail FA, Abboud E. Malignant transformation of uterine leiomyoma. Qatar Med J. 2012;2012(2):71-4
9. Murphy AA, Morales AJ, Ketel LM, Yen SS, Regression of Uterine Leiomyomata to the Anti progesterone RU486: dose response effect. Fertil steril 1995;64:187-90.
10. Wilson EA, Yang F, Rees ED. Estradiol and progesterone binding in uterine leiomyomata and in normal uterine tissues. Obstetrics Gynecology. 1980;55(1): 20-24.
11. Brandon DD, Bethea CL, Strawn EY, et al. Progesterone receptor messenger ribonucleic acid and protein are expressed in uterine leiomyomas. Am J Obstet Gynecol 1993;169:78.
12. Rein MS. Advances in uterine leiomyomata research: the progesterone hypothesis. Environ Health Perspect 2000;108 (suppl): 791-3.
13. Baulieu EE, The steroid hormone antagonist RU486 mechanism at the cellular level and clinical application. Endocrinol Metab Clin North Am. 1991 Dec; 20(4): 873-91