International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 2 Issue 6‖ June2013 ‖ PP.32-38

A Prospective Randomized Comparative Study Of Letrozole Vs Leuprolide Acetate In Symptomatic Relief Of Endometriosis.

[1]Partha sarathi Mitra, [2]Hasibul Hassan Sirazee, [3]B.V. Latha, [4]Mandira Dasgupta, [5]Sudhir adhikari

[1]RMO cum Clinical Tutor, Department of Obstetrics and Gynaecology, Medical College Hospital, Kolkata, 88, College Street, Kolkata-700073, West Bengal, India,
[2] Assistant Professor, Department of Obstetrics and Gynaecology, Medical College Hospital, Kolkata, India
[3]Resident, Deptt. Of Obstetrics & Gynecology, Medical College Hospital, Kolkata, India
4Associate Professor, Department of Obstetrics and Gynecology, Medical College Hospital, kolkata.
[5]Professor, Department of Obstetrics and Gynecology, Medical College Hospital, kolkata.

ABSTRACT: INTRODUCTION: *This prospective randomized comparative study was conducted to evaluate and compare the efficacy and tolerability of aromatase inhibitor Letrozole acetate versus GnRH agonist Leuprolide in managing chronic pelvic pain in women with clinically suspected endometriosis.*
METHODOLOGY: *Non pregnant women from 18-45 years of age with symptomatic (pain) endometriosis weer randomized to open label treatment of depot Leuprolide (3.75/mo) or Letrozole 2.5mg once daily for three months. A visual analog pain scale from 1-10 was used to assess the severity of pain.*
RESULTS: *50 women were randomized and all of them completed the study. No statistical or clinical significant difference on symptomatic relief was seen. Incidence of adverse events slightly higher in the Leuprolide group. But overall, satisfactory pain relief was achieved in only 36% of the total patients.*
DISCUSSION: *The main complaints of study participants are chronic pelvic pain and dysmenorrhoea. Our results show that mean decrease of VAS scores before and after 3 months of treatment with either drug was highly significant i.e. both treatments were effective. On comparison of both groups against each other, there was no significant difference i.e. both treatments were equally effective. We would recommend the treatment of endometriosis with letrozole because of the better side effect profile.*
CONCLUSION: *Both drugs are equally efficacious and safe in treating endometriosis associated pain. Letrozole has lesser adverse effects compared to Leuprolide. Other drugs or drug combinations need to be investigated for better pain relief.*
KEY WORDS: *Leuprolide, Letrozole, Endometriosis.*

I. INTRODUCTION

Endometriosis is defined as the presence of functioning endometrium (glands and stroma) in sites other than uterine mucosa like myometrium, called endometriosis interna or adenomyosis and at sites other than uterus, called endometriosis externa. The common abdominal structures involved in order of frequency are ovaries, pouch of Douglas, utero-sacral ligaments, broad ligaments, rectovaginal septum and pelvic lymph nodes. The rare sites are gut, appendix, ureter and urinary bladder. The common extra abdominal sites are abdominal scar of hysterotomy, ceaserean section, tubectomy and myomectomy, umbilicus, episiotomy scar, vagina and cervix. The remote sites are pleura, lungs and brain[1, 2]. In a review of endometriosis by Engemise et al, endometriosis can be associated with many distressing and debilitating symptoms, such as dysmenorrhea, abnormal menstruation (menorrhagia, polymenorrhoea, pre-menstrual spotting) infertility, dyspareunia, non-cyclical chronic pelvic pain, abdominal pain and other symptoms related to the organ involved like bladder (frequency, dysuria and hematuria), sigmoid colon and rectum (dyschezia, rectal bleeding, malena) or it may be asymptomatic, and incidentally discovered at laparoscopy or exploratory surgery [3]

According to the ACOG practice bulletin, endometrium requires estrogen for its continued growth and is a progressive disease. The aim of the hormonal treatment is to induce atrophy of the endometriotic implants. Various treatment options include expectant management, analgesia, hormonal-medical therapy, combined estrogen-progestin pills cyclic or continuous, gonadotropin releasing hormone (GnRH) agonists, progestins, given by an oral, parenteral, or intrauterine route, danazol, aromatase inhibitors or surgical intervention[4]. The traditional GnRH analogues aim at managing and improving the symptoms related to the disease, by producing a state of hypo-estrogenic state. But unfortunately it causes many unpleasant and unwanted side

effects to decrease the patient compliance, specially in chronically administered ones. So a better alternative would be welcome in such a situation[5].

Aromatase p-450 is the key enzyme for estrogen biosynthesis as it catalyzes conversion of androstenedione and testosterone to estrone and estradiol (E2) and is consistently found in endometriotic lesions and may be involved in the pathogenesis, promoting survival and growth[6]. Aromatase inhibitors suppress estrogen production in peripheral tissues to decrease circulating estrogen levels considerably. So a molecular basis for the use of aromatase inhibitors to treat endometriosis exists. This study was undertaken to compare Aromatase inhibitor, Letrozole against GnRH analogue Leuprolide acetate and evaluate its short term efficacy in causing symptomatic relief of endometriosis associated pain and analyze the patient compliance and adverse effects.

II. METHODOLOGY

We conducted a prospective randomized comparative study in the Department of Obstetrics and Gynecology, Medical College, Kolkata during 1st June 2011 - 31st May 2012 after approval by the Institutional Ethics Committee. Fifty women were recruited after diagnosis by laparoscopy / laparotomy. The inclusion criteria were presence of pain and menstrual disorder related to endometriosis and absence of any other complementary medical therapy for pain relief. The exclusion criteria were patients with endometriosis whose main symptoms pertain to infertility, symptoms not pertaining to that of endometriosis, women with other simulating illness like irritable bowel syndrome and presence of any other systemic illness. The recruited patients were enrolled with written informed consent. They were randomly divided by simple random sampling into two groups based on a table of random numbers. The table of numbers was generated with R (ver.2.13.1). The odd number patients on the random number table list were assigned to the Leuprolide group (Group-1: 25 patients were treated with leuprolide acetate depot 3.75 mg intramuscularly every four weeks for 3 months) and even numbered patients to the Letrozole group (Group-2: 25 patients were treated with letrozole tablets 2.5 mg orally daily for 3 months). Patients' compliance was ascertained by means of a Self Administered Questionnaire (SAQ) given to them. Both groups were followed up for a period of 3 months and the primary outcome in both groups was observed by measuring the efficacy in terms of symptomatic pain relief in each group by means of a visual analog scale and in terms of other parameters like relief of menstrual irregularities, failure of medical intervention leading to ultimate surgical management like hysterectomy and compliance and acceptability. Study Tools are laparoscopy, laparotomy, visual analogue scale and menstrual history.

Results were compiled and analyzed using R: A Statistical Package (ver. 2.15.1) and (MS-Excel ver.2010). Tests for means were conducted using R. If it was found significant (α value = 0.05 and β = 80% power) at these values the effect of the differences between interventions were calculated. Shapiro-Wilk test for normality was used and if the data was found to be normally distributed Student's T-test was used. For other data, a non-parametric Mann-Whitney's test was used to check for significance. Here if significance was ascertained the difference between medians was used to measure the difference between outcomes. Chi-squared test was used to check significance when categorical data of more than one variable was compared. Also a two-way table (also known as contingency tables) was employed to display and compare the results.

III. RESULT ANALYSIS

This study involved two groups comprising of 25 patients in each randomly divided by simple random sampling into two groups recruited after diagnosis by laparoscopy / laparotomy. The demographic distribution of the patients is shown in Table-1. Patients above 30 formed the bulk (82%). Most of the patients were married (94%). Urban population constituted 76% of the total. 72% women were at least secondary standard educated. Women with one or two child constituted a bulk (82%) of the study population with a decline in proportion of women with higher orders of parity possibly due to the disease pattern. The patients were more or less comparatively distributed between the groups Table-1. Intractable chronic pelvic pain was the major compliant in 60% of the patients. 22% presented with dysmenorrhea and dyspareunia. Women with abnormal menstrual patterns constituted 54% of the study population i.e. menorrhagia, the predominant abnormality, followed by polymenorrhoea and epimenorrhagia. The symptoms were comparable across the groups. 76% of the patients had no significant medical history, history of LSCS and D/E were found in the rest. Anemia was found in 48% women. The CA-125 was raised (>35) in 60% patients before treatment and was distributed across the groups. Table-1

The effect of both drugs on deep pelvic pain as recorded by Visual Analog Scale score (VAS), before and after 3 months of treatment the mean decrease is 3.86 ($t = 9.38$; 95% CI = 3.09 – 4.83) and 4.32 ($t = 13.08$; 95% CI = 3.64 – 5.00) in the Leuprolide and Letrozole groups respectively and were highly significant ($p \leq 0.01$). The difference of mean decrease between two groups is 0.36 (95% CI: -1.42–0.70; $t = 0.70$) ($p=0.49$) and hence no significant difference between the two groups in terms of effect on VAS. Table- 2, Fig-1. The mean

decrease of CA-125 level is 27.88 (95% CI = 23.09 – 34.83) ($p \leq 0.01$) and 26.26 (95% CI = 16.01 – 38.83) ($p \leq 0.01$) in the Leuprolide and Letrozole groups respectively and were highly significant.
The difference of mean decrease in CA-125 levels between leuprolide and letrozole is 1.62 (95% CI: -3.42–3.70) ($p = 0.66$). So there was no difference between the groups in terms of effect on CA-125 levels. Table-2, Fig-2Treatment with both drugs decreased the prevalence of menstrual abnormalities in study subjects which was not statistically significant ($p= 0.14$) on Chi Square test.Table-3, Fig-3. The difference in serum cholesterol before and after study was 3.56 (95% CI: -3.82–10.94) and 6.98 (95% CI: -4.18–11.66) in Leuprolide and Letrozole groups respectively and were not significant. Changes in triglyceride levels take place over a significantly longer time than the study period of three months. The difference in levels before and after the study was 4.6 (95% CI: -2.72–11.92) and 3.96 (95% CI: -2.98–11.21) respectively and were also insignificant ($p=0.47$).Table-2, Fig-4

The relative risk of CNS adverse effects (headache 28%, depression 8%, insomnia4%, fatigue12%, dizziness/vertigo10%) and hot flushes are 0.2 (95% CI: 0.02 – 1.6) and 1.62 (95% CI: 0.82 – 3.22) respectively when letrozole is compared to leuprolide thus favoring treatment with letrozole. The relative risk of GI adverse effects (Nausea/vomiting18%, altered bowel function20%) and Bone and joint pain between leuprolide and letrozole are 0.78 (95% CI: -0.34 – 1.76) and 0.67 (95% CI: -0.21 – 2.08) respectively favoring neither treatment. Table-4, Fig-5. There was a high incidence of leuprolide injection site reactions (60%). 10% of the patients described the pain as severe and recurrence at interval of 2-3 weeks. 68% women required additional pain killers. 64% of the total study subjects were not satisfied with the treatment. Three patients (2 in leuprolide and 1 in letrozole group) opted for surgical treatment during the course of the study. One of the patients in the Letrozole group became pregnant.

IV. DISCUSSION

The etiology-patho-physiology of endometriosis is not well understood because of the lack of a suitable animal model on which the anatomic correlates and natural history of disease could be studied(4). Endometriosis usually causes pain symptoms such as dysmenorrhea, deep dyspareunia and chronic pelvic pain. Although complete excision of endometriotic nodules may determine a significant improvement in pain symptoms, this surgery may be technically demanding, deep lesions might not be completely excised and there are risk of severe urological & colorectal complications [7]. The hormonal responsiveness of the implants can be exploited and provides the rationale for current methods of medical therapy. The search for the perfect medical treatment remains elusive. In this study we have compared the efficacy and safety of GnRH agonist leuprolide vs aromatase inhibitor letrozole. The safety of both groups of drugs has been well established in multiple studies but there are no studies directly comparing leuprolide against letrozole in short term treatment of endometriosis [8].

Endometriosis occurs during the active reproductive period [9]. The National Hospital Discharge Survey suggested that the incidence of endometriosis requiring hospitalization peaked between the ages of 40 and 44 years [10]. In our study maximum (52%) patients are between 30 & 35 years and 10% are between 40 and 44 years. In our study 52% of the women has a single child or less, 76% were between the ages of 30 to 40 and 94% were married women. Educated patients understand complex diseases like endometriosis better and are more compliant. They also conceive later increasing the chances of endometriosis. In our study 66% of the participants had at least level secondary education. This may have been a contributing factor Table-1. The main complaints of study participants are chronic pelvic pain (60%) and dysmenorrhoea (22%) etc. Our results show that mean decrease of VAS scores before and after 3 months of treatment with either drug was highly significant i.e. both treatments were effective. On comparison of both groups against each other, there was no significant difference i.e. both treatments were equally effective. CA-125 level before and after 3 months treatment show the median decrease in both groups were highly significant On comparison of both groups against each other, there was no significant difference. There was no correlation between decrease in CA-125 levels and VAS scores. The correlation coefficient, R^2 was 0.22.

With respect to the adverse effects studied, hot flushes were more in the case of GnRH analog treatment. The short duration of follow-up possibly biased the results of incidence of bone-pain in the letrozole group towards a null difference.In an open-label, phase 2, non-randomised prospective study, Ailawadi et al. examined the efficacy of letrozole in reproductive age women with endometriosis and chronic pelvic pain refractory to surgical and medical (leuprolide acetate for 3-6 months) treatment. After a diagnostic laparoscopy Letrozole (2.5 mg/day) and norethisterone acetate were administered in 10 patients for 6 months. During the first month, pain score improved in 9 patients (90.0%). At 6-months, there was a significant decrease in the intensity of pain symptoms. Only one patient (10.0%) had persistent pain. A second laparoscopy performed within 2 months of the completion of therapy demonstrated improved ASRM stage of endometriosis [11]. Another open-label, phase 2, non-randomized prospective study, Amsterdam et al. treated refractory endometriosis and

chronic pelvic pain with anastrazole (1 mg/day) and oral contraceptive pill on 18 women. 15 women (83.3%) completed the 6-month treatment. Improvements in pain symptoms were observed at 1 month and at completion, a significant reduction in pain intensity was reported in 14 of 15 patients (93.3%) [12]. Remorgida et al. administered letrozole (2.5 mg/day) and desogestrel to 12 women with refractory endometriosis-related pain. All the patients interrupted the treatment at median time of 84 days because of the development of functional ovarian cysts. Dyspareunia was significantly decreased but no statistically significant change was observed in the reported intensity of chronic pelvic pain. Pain recurred after discontinuation and at 6-month follow-up their intensity was similar to baseline values [13]. Treating chronic pain associated with endometriosis can be frustrating to both clinicians and patients, especially when it is recurrent or resistant to standard medical or surgical management. In vitro studies have shown that endometriotic tissue responds not only to the ovarian E2 but also to extra ovarian E2 synthesised by aromatase pathways [14]. GnRH analogues effectively down regulate ovaries and in turn ovarian E2 biosynthesis but have little effects on extra ovarian E2 production. Similarly, if we target extra ovarian E2 synthesis by aromatase inhibitors, it will in fact stimulate ovarian E2 production through follicular stimulating hormone (FSH) surge. So, in theory, aromatase inhibitors could be combined with GnRH analogues, it should prove very effective towards endometriosis regression by suppressing both ovarian and extra ovarian E2.

In view of the evidence presented above, we would recommend the treatment of endometriosis with letrozole because of the better side effect profile. But because of the high incidence of bone pain on treatments of 6 months duration, we would recommend additional daily calcium supplements and vitamin-D prophylaxis in patients treated with letrozole. There were several limitations in our study. The study was underpowered because of the small sample size. This was because of the strict inclusion criteria of laparoscopy/laparotomy confirmed endometriosis. Also the short duration of follow up may have biased the results towards favoring letrozole.

CONCLUSION

Endometriosis occurs in 7-10% of the general population. The dependence of endometriosis on the woman's cyclic production of menstrual cycle hormones provides the basis for medical therapy. Both GNRH agonist Leuprolide and aromatase inhibitor Letrozole are safe and equally efficacious when used for short term treatment of Endometriosis. There was no significant difference in efficacy (as measured by a Visual Analogue Scale, Menstrual pattern and CA-125 levels) between them. Median CA-125 levels decreased on treatment. But it did not correlate with the decrease in VAS. The adverse effect profile was better with letrozole than with leuprolide. Patients unable to tolerate Leuprolide can be switched to Letrozole without compromising the efficacy of the therapy. Leuprolide with add-back letrozole may be tried as a new avenue of multi-drug therapy for endometriosis.

REFERENCES

[1.] Olive DL, Schwartz LB. Endometriosis. N. Engl. J. Med. 1993 Jun 17;328(24):1759–69.

[2.] Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am. J. Epidemiol. 2004 Oct 15;160(8):784–96.

[3.] Engemise S, Gordon C, Konje JC. Endometriosis. BMJ. 2010;340:c2168.

[4.] ACOG practice bulletin. Medical management of endometriosis. Number 11, December 1999 (replaces Technical Bulletin Number 184, September 1993). Clinical management guidelines for obstetrician-gynecologists. Int J Gynaecol Obstet. 2000 Nov;71(2):183–96.

[5.] Howard FM. An evidence-based medicine approach to the treatment of endometriosis-associated chronic pelvic pain: placebo-controlled studies. J Am Assoc Gynecol Laparosc. 2000 Nov;7(4):477–88.

[6.] Ferrero S, Gillott DJ, Venturini PL, Remorgida V. Use of aromatase inhibitors to treat endometriosis-related pain symptoms: a systematic review. Reprod. Biol. Endocrinol. 2011;9:89.

[7.] Vercellini P, Crosignani PG, Somigliana E, Berlanda N, Barbara G, Fedele L. Medical treatment for rectovaginal endometriosis: what is the evidence? Hum. Reprod. 2009 Oct;24(10):2504–14.

[8.] Alborzi S, Hamedi B, Omidvar A, Dehbashi S, Alborzi S, Alborzi M. A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. Arch. Gynecol. Obstet. 2011 Jul;284(1):105–10.

[9.] Ranney B. Endometriosis. 3. Complete operations. Reasons, sequelae, treatment. Am. J. Obstet. Gynecol. 1971 Apr 15;109(8):1137–44.

[10.] Eyster KM, Klinkova O, Kennedy V, Hansen KA. Whole genome deoxyribonucleic acid microarray analysis of gene expression in ectopic versus eutopic endometrium. Fertil. Steril. 2007 Dec;88(6):1505–33.

[11.] Ailawadi RK, Jobanputra S, Kataria M, Gurates B, Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil. Steril. 2004 Feb;81(2):290–6.

[12.] Amsterdam LL, Gentry W, Jobanputra S, Wolf M, Rubin SD, Bulun SE. Anastrazole and oral contraceptives: a novel treatment for endometriosis. Fertil. Steril. 2005 Aug;84(2):300–4.

[13.] Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Hum. Reprod. 2009 Dec;24(12):3033–41.

[14.] Matalliotakis I, Cakmak H, Dermitzaki D, Zervoudis S, Goumenou A, Fragouli Y. Increased rate of endometriosis and spontaneous abortion in an in vitro fertilization program: no correlation with epidemiological factors. Gynecol. Endocrinol. 2008 Apr;24(4):194–8.

Table - 1 Demographic and Clinical Status of the Study Groups

Demographic Status		
	Leuprolide n=25	Letrozole n=25
Age <30	02	05
30- 35	14	12
35- 40	07	05
>40	02	03
Marital Status		
Married	23	24
Unmarried	02	01
Residence		
Rural	05	07
Urban	20	18
Education		
Higher secondary	13	07
Secondary	03	10
Primary	05	04
Illiterate	04	04

Clinical Status		
Parity Nullipara	02	01
Multipara	23	24
Pain Chr pelvic pain	14	16
Dysmenorrhoea	06	07
Dyspareunea	05	02
Menstruation Normal	12	15
Abnormal	13	10
H/O Scarred uterus	03	08
Unscarred uterus	22	17

Investigation		
Hemoglobin < 10	13	14
> 10	12	11
CA-125 < 35	08	12
> 35	17	13

Table – 2 Comparison of Before and After Treatment effect of Leuprolide and Letrozole in respect of different parameters and statistical analysis

	Leuprolide n=25				Letrozole n=25				Comparison between Leuprolide & Letrozole	
	Before T/t mean	After T/t	Diff. of mean	p-value	Before T/t	After T/t	Diff. of mean	p-value	difference of mean decrease	p-value
VAS	7.2± 1.29	3.24±2.13	3.86	≤ 0.01	7.12±1.48	2.80±1.68	4.32	≤ 0.01	0.36	0.49
CA-125	45.2 ±16.2	17.0±5.5	27.8	≤ 0.01	43.6±21.4	17.3±8.44	26.2	≤ 0.01	1.62	0.66
Chl	155.2±15.8	151.6 ±13.5	3.56	0.33	157.6±15.6	150.7 ±16.2	6.98	0.07		
TG	87.92±10.9	83.32±13.4	4.6	0.21	86.84±11.2	84.04±14.2	3.96	0.47		

Table – 3 Improvement of menstrual pattern as a result of Leuprolide and Letrozole

Menstrual pattern		Leuprolide n=25	Letrozole n=25
Before T/t	Abnormal	13	10
	Normal	12	15
After T/t	Abnormal	05	05
	Normal	20	20

Table – 4 Side effects noted in the study groups receiving Leuprolide and Letrozole

	Leuprolide n=25	Letrozole n=25
CNS adverse effect	13	08
Hot Flushes	05	01
GI adverse effect	07	09
Bone and joint pain	04	06
Patient satisfaction	10	08

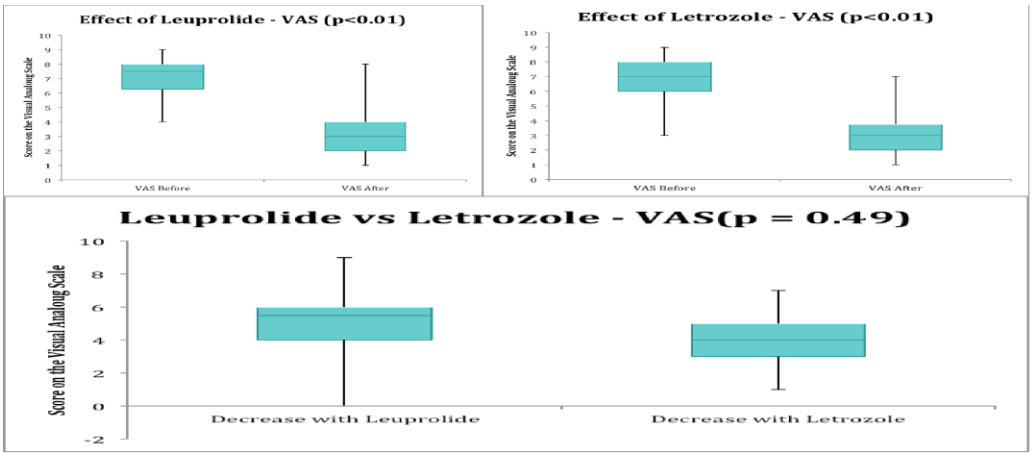

Fig-1: Boxplots showing VAS before & after treatment in both Leuprolide & Letrozole group and also comparison of the effect of Leuprolide & Letrozole based on VAS.

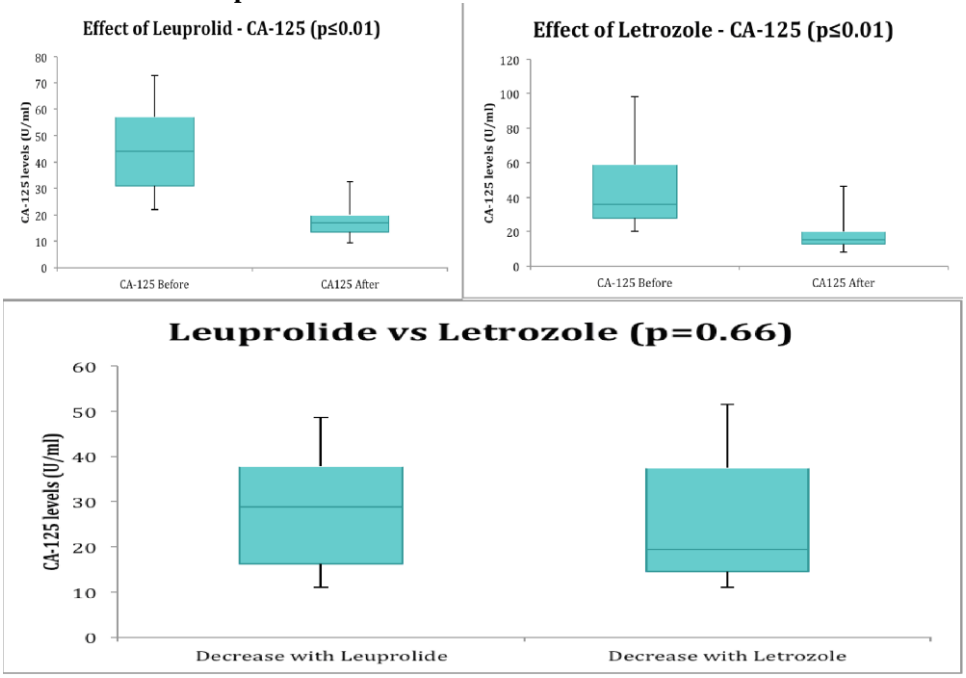

Fig-2: Boxplots showing CA-125 levels before & after treatment in both Leuprolide & Letrozole group and also Comparison of the effect of Leuprolide & Letrozole based on CA-125 levels.

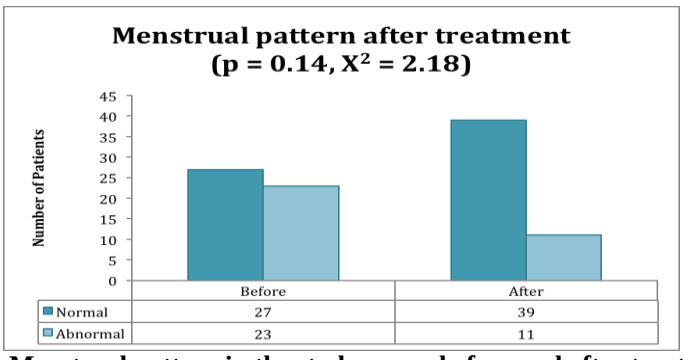

Fig-3: Menstrual pattern in the study group before and after treatment.

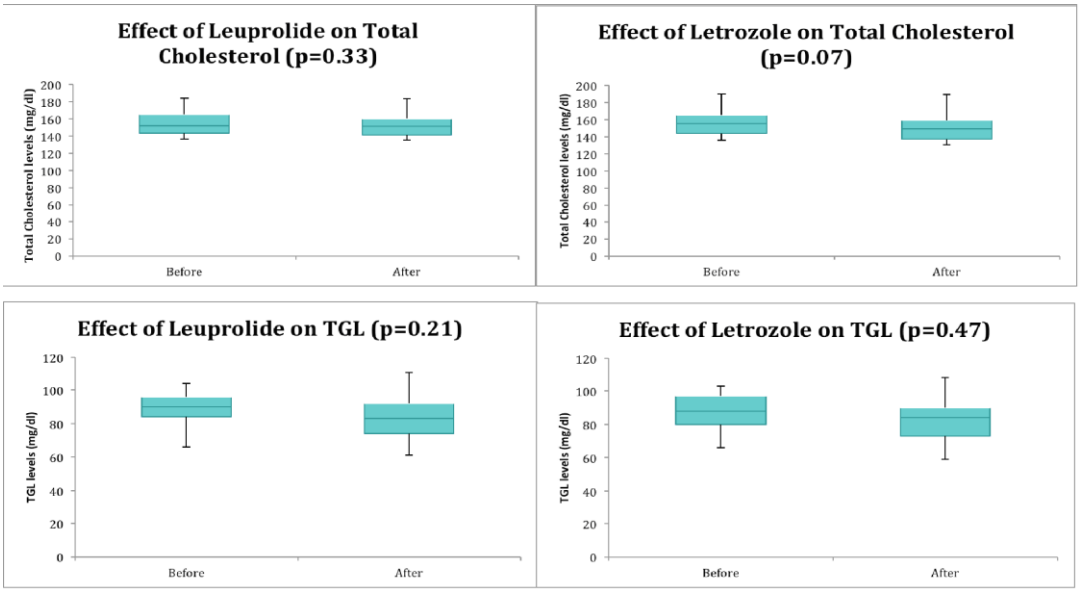

Fig- 4: Boxplot showing serum Cholesterol and Triglyceride levels before & after treatment in both Leuprolide & Letrozole group.

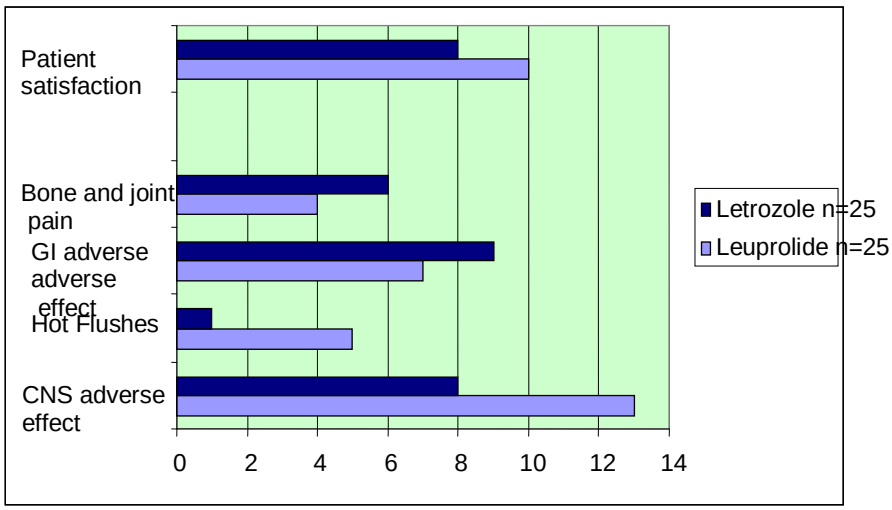

Fig-5: Chart compares patient satisfaction and incidence of side effects between Leuprolide & Letrozole group.