CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3732532

Available online at: http://www.iajps.com ***Research Article***

ENDOMETRIOSIS: ROLE OF DANAZOL VERSUS LETROZOLE FOR THE MANAGEMENT OF ENDOMETRIOSIS

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Article Received: January 2020 **Accepted:** February 2020 **Published:** March 2020

Abstract:

Objective: *Objective of this study is to compare the mean decrease in VAS pain score with Danazol versus Letrozole for the management of females presented with endometriosis.* ***Study design:*** *Randomized controlled trial.* ***Setting:*** *Department of Obstetrics and Gynaecology, Lady Wallington Hospital, Lahore.* ***Duration of study:*** *Six months after approval of synopsis.****Patients and Methods:*** *The sample size of 150 cases; 75 cases in each group is calculated with 95% confidence level, 80% power of test and taking expected mean±s.d of mean decrease in VAS pain score i.e. 0.26±1.968 with Latraterzaol and -1.61±2.4 with Danazol for the management of females presented with endometriosis. Sampling technique was Non probability, purposive sampling. Inclusion criteria was, females of age 20-40 years with diagnosis of endometeriosis. 150 females fulfilling inclusion criteria was registered through OPD of Lady Wallington Hospital, Lahore. Informed consent was taken. Demographic history including name, age, parity and duration of pain will also be obtained. Females was randomly divided in two groups through lottery method. Females in group A will receive treatment with Letrozole tablets (2.5 mg/day) from the third day of the first menstrual cycle. Females in group B will receive Danazol tablets (600 mg/day). Pelvic pain was assessed by using VAS score. Then females in each group was prescribed medication and followed up in OPD for 3 months. Pelvic pain after 3 months was again noted. All the information was collected on a specially designed proforma. All the collected data was entered into SPSS version 16 and analyzed through it. Variable like parity was presented as frequency distribution. Quantitative data like age, duration of pelvic pain and pain score before and after 3 months was presented as means and standard deviations. Mean decrease in pain score was calculated by subtracting post-treatment VAS pain score from pre-treatment VAS pain score. The two groups was compared for mean decrease in VAS pain score by using Student T-test. P-value ≤ 0.05 was taken as significant. Data was stratified for the duration of pelvic pain to address the effect modifiers.* ***Results:****There were total 150 cases who were enrolled in this study. The mean age of the patients was 29.99±5.80. The mean pain score evaluated before the time of treatment was noted that was 4.44±1.73. After 3 months of treatment the mean pain score was 2.40±1.04 with a mean decrease in pain score of 20.4±1.54 (p-value=0.00). This difference in pain score was significantly different for the both treatment group.* ***Conclusion:*** *There is significant difference in mean decrease in pain score in both groups.*

Key words*: Danazole, Letrozole, Endometriosis, Pelvic Pain.*

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Please cite this article in press Asma Qayyum et al., ***Endometriosis: Role Of Danazol Versus Letrozole For The Management Of Endometriosis,****Indo Am. J. P. Sci, 2020; 07(03).*

INTRODUCTION:

Endometriosis is an estrogen-dependent disease characterized by the presence of functional endometrial tissue outside the uterus. It is an important cause of long-term morbidity, commonly from chronic pelvic pain and infertility.[1] The disorder is encountered in 7-10% of actively menstruating women, with a suspected prevalence as high as 22% in asymptomatic women, 60% in women with dysmenorrhoea and 30% in women with subfertility.[2] It is an important cause of chronic pelvic pain. [3]

Both, medical and surgical therapy is usually complimentary for endometriosis. Laparoscopy is the treatment of choice.[4] Endometriosis tissue has the potential for aromatase gene expression that leads to aromatase and estrogen production. The medical treatment is used to prevent the stimulation of the endometrial tissue by the suppression of the estrogen secretion or antagonizing the estrogen action.[5]

Danazol, a synthetic androgen, has been studied as a treatment for endometriosis since 1980. Danazol inhibits estrogen production via inhibition of the hypothalamic-pituitary-ovarian axis.Approximately half of patients with chronic pain associated with endometriosis are refractory to currently available conventional medical treatments (including, GnRH, oral contraceptives and Danazol).[3]

In a study by Roghaei, et al,Danazol was compared with Letrozole among 38 patients in each group with endometriosis. The results of this study showed mean pelvic pain score between both groups at baseline was 1.14±2.80 in Letrozole group versus 0.50±3.00 in Danazol group. At three months after treatment mean pelvic pain score was 0.88±0.82 and 2.11±0.60. Mean decrease/change in pain score was 0.26±1.98 versus -1.61±2.4 respectively.[6] Another study done by Ferrero etal on 26 patients with endometriosis demonstrated that Danazol can significantly reduce the chronic pelvic pain at 3-months treatment course i.e. mean pelvic pain score at baseline of these patients was 6.0±1.3 and at 3-months of treatment was 3.4±1.8. Mean decrease in VAS pain score was 2.6±0.5. [(7)] Similarly, a recent study published in March 2014 on 20 patients with endometriosis showed that pre-treatment pain score was 7.65±1.35 and at 6-months after treatment was 6.1±1.2. Mean decrease in VAS pain score was 1.55±0.15.[(8)]

The rationale of this study is to compare the mean decrease in pain score with Danazol versus Letrozole for the management of females presented with endometriosis. Both drugs are easily available in market and are often recommended by gynecologists. But some above mentioned studies has reported that Letrozole is more beneficial as compared to Danazol. On contrary some studies showed Danazol can significantly reduce the pelvic pain. Due to lack of international evidence and unavailability of local studies we are unable to recommend the best drug for better management of endometriosis. There is only one study reported earlier which compare Letrozole and danazole and was conducted on small sample size i.e. < 40 cases in each group. I will conduct this study on large sample size to achieve more precise results. That is why we have designed this study to compare Letrozole with Danazol for the management of endometriosis

Study design: Randomized controlled trial
Setting: Department of Obstetrics and Gynecology, Lady Wallington Hospital, Lahore
Sample size: The sample size of 150 cases; 75 cases in each group is calculated with 95% confidence level, 80% power of test and taking expected mean±s.d of mean decrease in VAS pain score i.e. 0.26±1.968 with Latraterzaol and -1.61±2.4 with Danazol for the management of females presented with endometriosis.

Sample technique: Non probability, purposive sampling

Duration of study: Six months after approval of synopsis.

Inclusion criteria
Females of age 20-40 years with diagnosis of endometeriosis (as per operational definition)

Exclusion criteria
Undiagnosed vaginal bleeding (on clinical examination)
Endometriomas >2cm (on USG)
Sensitivity to letrozole or Danazole (through history)
Seizure disorder (history of fits)
Pregnancy
Cardiac problem (abnormal ECG), renal disease (serum creatinine>1.2gm/dl) or hepatic disease (ALT>40IU, AST>40IU).

Data Collection Procedure: 150 females fulfilling inclusion criteria was registered through OPD of Lady Wallington Hospital, Lahore. Informed consent was taken. Demographic history including name, age, parity and duration of pain will also be obtained. Females was randomly divided in two groups through lottery method. Females in group A will receive treatment with Letrozole tablets (2.5 mg/day) from the third day of the first menstrual cycle. Females in group B will receive Danazol tablets (600 mg/day). Pelvic pain was assessed by using VAS score. Then females in each group was

prescribed medication and followed up in OPD for 3 months. Pelvic pain after 3 months was again noted. All the information was collected on a specially designed proforma (attached).

Data Analysis: All the collected data was entered into SPSS version 16 and analyzed through it. Variable like parity was presented as frequency distribution. Quantitative data like age, duration of pelvic pain and pain score before and after 3 months was presented as means and standard deviations. Mean decrease in pain score was calculated by subtracting post-treatment VAS pain score from pre-treatment VAS pain score. The two groups was compared for mean decrease in VAS pain score by using Student T-test. P-value $\leq$ 0.05 was taken as significant. Data was stratified for the duration of pelvic pain to address the effect modifiers.

RESULTS:

There were total 150 cases who were enrolled in this study. The mean age of the patients was 29.99±5.80. Mean pain score before treatment in Letrozole group was 3.04±1.01 while in danazole group the mean pain score before treatment was 5.05±1.02. After 3 months of treatment the mean pain score was in Letrozole group: 2.01±0.95 and Danazole group: 2.78±0.99. The mean decrease in pain score in Letrozole group was 1.02±1.09 while in Danazole group 3.06±1.23 (p-value=0.00). This difference in pain score was significantly different for the both treatment groups.

Table # 1
Distribution for Age

Total	Mean	Standard deviation
150	29.99	5.80

Table # 2
Distribution for Pain score pre treatment

Total	Mean	Standard deviation
150	4.44	1.73

Table # 3
Pain score before treatment in groups

Group of patients	Mean	N	Std. Deviation
Lataterzaol	3.0400	75	1.01927
Danazol	5.8533	75	1.02263

Table# 4
Distribution for Post treatment Pain Score

Total	Mean	Standard deviation
150	2.40	1.04

Table # 5
Pain score after treatment in both groups

Group of patients	Mean	N	Std. Deviation
Lataterzaol	2.0133	75	.95143
Danazol	2.7867	75	.99040

Table# 6
Distribution for difference in Pain Score

Total	Mean	Standard deviation
150	2.04	1.54

Table# 7
Distribution for Parity

Parity of women		
	Frequency	Percent
1.00	18	12.0
2.00	49	32.7
3.00	37	24.7
4.00	26	17.3
5.00	12	8.0
6.00	8	5.3
Total	150	100.0

Table # 8
Mean Difference in Pain Score in both groups

	Group of patients	N	Mean	Std. Deviation
Difference in Pain score	Lataterzaol	75	1.0267	1.09017
	Danazol	75	3.0667	1.23391

P-value= 0.000

DISCUSSION:

Current evidence showed that about half of patients with chronic pelvic pain related to endometriosis are resistant to current available treatments that create a hypoestrogenic state [89, 90.] And even with conservative surgery endometriosis often recurs with pain remaining resistant to repeated surgical attempts and an overall immediate response of chronic pain to surgery about 50%. [91]

Hormonal therapies are not curative of endometriosis; therefore, they should be chronically administered to women with endometriosis [92]. Viewed from this perspective, the incidence of adverse effects is particularly relevant because they may affect compliance to therapy. This randomized prospective study compared two different therapeutic regimens, demonstrating that co-treatment with progestin is more accepted by the patients that co-treatment with gonadotropin-releasing hormone analogue. In fact, the incidence of adverse effect is significantly higher when letrozole is combined with triptorelin than when it is combined with norethisterone acetate. In fact, 77.8% of women included in group T and 35.3% of those included in group N had at least one adverse effect. In line with this, the percentage of patients who interrupted the treatment was significantly higher in group T than in group N (44.4% versus 5.9%). Because of these reasons, the study was terminated before it reached the full enrolment of 80 subjects

The risk of adverse effects during treatment with aromatase inhibitors is related to the length of treatment. A short-term administration of aromatase inhibitors (two or three months) may not cause significant adverse effects; in the current study only two women (5.7%) interrupted the treatment before the fourth month of therapy because of adverse effects. This observation is consistent with a recent study which reported no significant adverse effect of administering letrozole for two months after laparoscopic treatment of endometriosis 93. However, several previous studies showed that a longer administration of aromatase inhibitors (six months) might be associated with several adverse effects. 94, 95

Consistent results have been reported in multiple case reports and case series, [96, 97]. Shippen and West, [98] have reported a rapid, progressive reduction in symptoms over 3 months, with the maintenance of remission of symptoms for more than 24 months after treatment of two sisters with premenopausal endometriosis with anastrozole (1 mg/d), together with oral progestin (200 mg/d). Also, other two previous case reports have shown successful pain relief and reduction of lesion size with the use of aromatase inhibitor alone (anastrozole or letrozole) for 9 months[97].

Another consistent result has been reported by Verma and Konje[99] in their case series. They have treated four premenopausal women with endometriosis associated with chronic pelvic pain refractory to conventional treatment using aromatase inhibitors for 6 months which has resulted in a marked improvement in pelvic pain and their mean pain score fell from 9 prior to treatment to 4.5 at the end of treatment. However – unlike the current study-three months after

treatment two patients have re-elevation of their pain score and were worried that their pain may get worse.

In a recent report of five premenopausal patients with documented ovarian endometriomas and chronic pelvic pain resistant to conventional medical and surgical treatment, Seal et al., have found that treatment of letrozole 2.5 mg in addition to one tablet of 0.15 mg of desogestrel, 0.03 mg of ethinyl estradiol, calcium (1200 mg), and vitamin D3 (800 IU) daily for 6 months has resulted in the disappearance of ovarian endometrioma and reduction in pelvic pain in all cases at the end of 6 months with a significant reduction of pain scores only after 1 month of treatment.

In a previous pilot prospective study there was 100% pain relief and 90% reduction in lesion size when 10 premenopausal women with endometriosis not responding to surgical or medical treatment were treated with letrozole and norethindrone acetate for 6 months.[100] In the present we did not comment on lesion size and we were more concerned with the problem of chronic pelvic pain related to endometriosis. There was significant difference was noted in two drugs in our study. [100,101,96,97]

Similar findings have been found by Soysal et al.[101]

CONCLUSION:

There is significant difference in mean score between two groups in terms of decrease in pain score. There is more decrease in pain score by danazole as compared to latrazole. So, it is clear that danazole should be recommended for the endometriosis related pelvic pain.

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