

Research Article



Comparison of Letrozole versus Danazol for the Pain Management of Females Presented with Endometriosis

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Abstract | Endometriosis is an estrogen-regulated disease, and is signified by the existence of a particular endometrial tissue exterior to the uterus. It is a principal cause of long lasting morbidity, mostly from serious pelvic pain⁽¹⁾. Endometriotic tissue has the potential for aromatase gene expression that leads to aromatase and estrogen production. Danazol is a synthetic androgen whereas Letrozole is aromatase inhibitor. This study was conducted to compare the mean decrease in visual analogue scale (VAS) pain score with Danazol versus Letrozole for the pain management of endometriosis in females. A total of 140 females fulfilling inclusion criteria were registered and a non-probability purposive technique of sampling was used. Diagnostic laparoscopy was conducted to make a diagnosis of endometriosis. Females were divided into two groups. Females in group A received treatment with Letrozole tablets (2.5 mg/day) and in group B received Danazol tablets (600 mg/day) for 3 months. Pelvic pain was assessed using VAS score and the mean decrease in pain score was assessed between two groups using independent sample student t-test. Results of this study demonstrate that the mean age of the patients was 29.99±5.80 and the mean pain score before treatment in Letrozole group was 3.04±1.01 while in Danazol group was 5.05±1.02. Post-three months of treatments, mean pain score was 2.01±0.95 and 2.78±0.99 in Letrozole and Danazol groups, respectively. The mean decrease in pain score in Letrozole group was 1.02±1.09 (p-value=0.00) while in Danazol group; it was 3.06±1.23 (p-value=0.00). This difference in pain score was considerably different in both treatment groups. A higher decrease in pain score was observed in Danazol compared to Letrozole treated groups.

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Introduction

Endometriosis is a painful disorder, and estrogen dependent disease, which is characterized by the presence of functional endometrial tissue, in sites other than uterine cavity, such as fallopian tubes, ovaries, other pelvic and extra pelvic sites. Endometriosis is a significant cause of long-term morbidity, usually from infertility, dysmenorrhea and chronic pelvic pain.^{(1), (2)}

Both, medical and surgical therapy is usually complementary for endometriosis. Laparoscopy is the gold standard for diagnosis.⁽³⁾ Endometriotic tissue has the potential for aromatase gene expression that leads to aromatase and estrogen production. The medical treatment is used to stop the stimulation of the endometrial tissue by the suppression of the estrogen secretion or antagonizing the estrogen action.⁽⁴⁾ Danazol, a synthetic androgen, has been diagnosed as a consideration for endometriosis since 1980. Dana-

zol inhibits the production of estrogen via inhibition of the hypothalamic-pituitary-ovarian axis.⁽²⁾ On the other hands, Letrozole is a non –steroidal, highly potent and well-tolerated competitive inhibitor of aromatase enzyme system.

In a study by Roghaei, et al, Danazol was compared with Letrozole among 38 patients in both groups with endometriosis. The results of this study showed mean pelvic pain score in Letrozole group at baseline (1.14±2.80 versus 0.50±3.00 in the Danazol group). At three months after treatment mean pelvic pain score in the Letrozole group was 0.88±0.82 and in the Danazol group it was 2.11±0.60. Mean decrease/change in pain score was 0.26±1.98 in Letrozole group versus -1.61±2.4 in Danazol group⁽⁵⁾. Another study done by Ferrero et al 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⁽⁶⁾.

Endometriosis is a disease that is most commonly seen during the reproductive years. It has been seen that endometriosis occurs in roughly 6–10% of actively menstruating women. Endometriosis may have diverse signs and symptoms. The most important symptom of endometriosis is chronic pelvic pain. The pain can be cramping or of sharp nature that involves both sides of the pelvis, the lower back and rectal area, and even in the legs. Endometriosis-related pain may have one of the following variety of presentations.^{(7),(8)}

Dysmenorrhea –Excruciating, many times impeding spasms during the menstruation.

Chronic pelvic pain –Usually accompanied by abdominal pain and lower back pain.

Dyspareunia – Painful sexual intercourse.

Dysuria – Urinary frequency, urgency, haematuria, and sometimes painful voiding.

- Females of age 20-35 years with diagnosis of endometriosis.
- Cyclic predictable menses.
- Endometriotic lesions documented by Ultrasonography and Laparoscopy.
- Chronic pelvic pain or dysmenorrhea experienced for at least two weeks in last three months.

Undiagnosed vaginal bleeding (on clinical examination, other than her normal periods).

- Endometriotic lesions > 2cm (on USG).
- Sensitivity to Letrozole or Danazol (through history).
- Seizure disorder
- Cardiac problem
- Renal disease.

The sample size of 140 cases; 70 cases in each group was calculated by using 10% level of significance, 90% power of test and taking expected mean ± S.D of mean decrease / change in VAS pain score i.e. 0.26 with Letrozole and 1.61 with Danazol for the pain management of females presenting with endometriosis.⁽⁶⁾

$$N = \frac{\delta^2 (Z_{1-\alpha} + Z_{1-\beta})^2}{(\mu_o - \mu_\alpha)^2}$$

Z_{1-α}: Confidence level 90% = 1.645; Z_{1-β}: Power of test 90%; μ_o: Population mean I = 0.26; μ_α: Population mean = 1.61; δ²: Variance; N: 140 Patients.

Method and Material

This randomized control trial was conducted from June 2015 to June 2016. A total of 140 females fulfilling inclusion criteria were registered through the outpatient department of Teaching Hospital, Lahore. Non-probability purposive technique of sampling was used for this study and informed consent was taken. Demographic history including name, age, parity and duration of pain was obtained. All the Patients underwent diagnostic laparoscopy to determine the grades of endometriosis. Females were randomly divided in two groups through lottery method. Females in group A received treatment with Letrozole tablets (2.5 mg/day) from the third day of the first menstrual cycle for 3 months. Females in group B received Danazol tablets (600 mg/day) for 3 months. Pelvic pain was assessed by using VAS (visual analogue scale) score. Then females in each group were prescribed medication and followed up in the outpatient department for 3 months. Pelvic pain after 3 months was again noted. Mean decrease in pain score was calculated by subtracting post-treatment VAS pain score from pre-treatment VAS pain score. The two groups were compared for mean decrease in VAS pain score by us-

ing Student t-test. P-value ≤ 0.05 was taken as significant. All the information was collected on a specially designed proforma.

All the collected data was entered and analyzed in the SPSS version 16. Variable-like parity was presented as frequency distribution. Quantitative data such as 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 were 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.

Results and Discussion

There were total 140 cases that were enrolled in this study. The mean age of the patients was 29.99 ± 5.80 . Mean pain score evaluated before the time of treatment in Letrozole group was 3.04 ± 1.01 while in Danazol group the mean pain score before treatment was 5.05 ± 1.02 . After 3 months of treatment the mean pain score in Letrozole group was 2.01 ± 0.95 , and Danazol group was 2.78 ± 0.99 . The mean decrease in pain score in Letrozole group was 1.02 ± 1.09 (p-value=0.00) while in Danazol group it was 3.06 ± 1.23 (p-value=0.00). This difference in pain score was notably different for both treatment groups.(Table 1)(Table 2)(Table 3).

Table 1: Distribution for pain score pretreatment.

| Total | Mean | Standard deviation |
|-------|------|--------------------|
| 140 | 4.44 | 1.73 |

Pain score before treatment in groups.

| Group of patients | Mean | N | Std. Deviation |
|-------------------|--------|----|----------------|
| Letrozole | 3.0400 | 70 | 1.01927 |
| Danazol | 5.8533 | 70 | 1.02263 |

Table 2: Distribution for post treatment pain score.

| Total | Mean | Standard deviation |
|-------|------|--------------------|
| 140 | 2.40 | 1.04 |

Pain score after treatment in both groups.

| Group of patients | Mean | N | Std. Deviation |
|-------------------|--------|----|----------------|
| Letrozole | 2.0133 | 70 | 0.95143 |
| Danazol | 2.7867 | 70 | 0.99040 |

Table 3: Mean Difference in Pain Score in both groups.

| | Group of patients | N | Mean | Std. Deviation |
|--------------------------|-------------------|----|--------|----------------|
| Difference in Pain score | Letrozole | 70 | 1.0267 | 1.09017 |
| | Danazol | 70 | 3.0667 | 1.23391 |

P-value: 0.000.

Endometriosis is a painful gynecological condition in which the cells from the inside layer of uterus, the endometrium, prosper and become visible outside the uterine cavity, most frequently on the membranes which outline the abdominal cavity such as peritoneum. There is no specific treatment for endometriosis, but it can be managed in a variety of ways, including different medications for pain, different hormonal treatments, and surgery.⁽⁹⁾

The risk of side effects during management with aromatase inhibitors is related to the treatment duration. A temporary treatment with aromatase inhibitors for 2 or 3 months may not cause any major side effects. In one study conducted by Riss BJ, just 2 women (5.7%) stop the treatment before the 4th month of therapy because of side effects. This finding is reliable with a latest study, which reported no major side effect of administering Letrozole for 2 months after laparoscopic management of endometriosis⁽¹⁰⁾. However, some earlier studies showed that a longer management of aromatase inhibitors for 6 months might be related with numerous side effects.^{(11),(12)} In a latest report of five premenopausal patients with recognized ovarian endometrium as and chronic pelvic pain opposing to conservative 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 brought about the disappearance of ovarian endometrioma and decrease in pelvic pain in all cases at the end of 6 months with a major decrease of pain scores only after 1 month of treatment. In a study by Roghaei, et al, Danazol was compared with Letrozole among 38 patients in each group with endometriosis. The outcome of this study showed mean pelvic pain score in Letrozole group at baseline was 1.14 ± 2.80 versus 0.50 ± 3.00 in the Danazol group. At three months after treatment mean pelvic pain score in Letrozole group was 0.88 ± 0.82 and in the Danazol group was 2.11 ± 0.60 . Mean decrease/change in pain score was 0.26 ± 1.98 versus -1.61 ± 2.4 respectively.⁽⁵⁾ Another study done by Ferrero et al on 26 patients with endo-

metriosis 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 ;⁽⁶⁾ but the sample size was small.

I will conduct this study on large sample size to achieve more precise results. This is why we have designed this study to compare Letrozole with Danazol for the management of endometriosis.

In our study, we did not remark on lesion size and we were more concerned with the matter of chronic pelvic pain related to endometriosis. 140 cases were enrolled in this study. According to the results mean decrease in pain score in Letrozole group was 1.02 ± 1.09 while in Danazol group was 3.06 ± 1.23 . There is more decrease in pain score with Danazol as compared to Letrozole. So there was significant difference noted in two drugs in our study.^{(13), (14), (15), (16)} However it had no effect on the course of illness or disease severity.

Conclusion

There is major difference in mean score between two groups in terms of decrease in pain score. There is more decrease in pain score by Danazol as compared to Letrozole treatments. Therefore, it is clear that Danazol should be recommended for the endometriosis related pelvic pain. Multi-centre studies are needed in future to further assess the impact of such treatments. It would help in the management of a debilitating problem in the society and may improve the wellbeing of woman in the country.

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