Pentoxifylline therapy after laparoscopic surgery for different stages of endometriosis: A prospective, double-blind, randomized, placebo-controlled study

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Abstract

STUDY OBJECTIVE: To evaluate the effects of pentoxifylline administration on patients with different stages of endometriosis on whom laparoscopy was performed.

DESIGN: Prospective, double-blind, randomized, placebo-controlled clinical (Canadian Task Force classification I).

SETTING: University and private hospitals.

PATIENTS: Eighty-eight women, all with infertility, some with dysmenorrhea, dyspareunia, or pelvic pain, on whom a laparoscopic diagnosis of endometriosis was made.

INTERVENTIONS: The treatment group received 800 mg pentoxifylline daily for 6 months immediately after surgery. The control group received placebo capsules. All patients were followed-up for 1 year thereafter.

MEASUREMENTS AND MAIN RESULTS: A comparison of pregnancy rate and recurrence of signs and symptoms in the 2 groups was performed. Forty-three patients were studied in the pentoxifylline group and 45 in the placebo group. The cumulative pregnancy rate was 39.5% and 35.6% in the treatment and control groups, respectively. The overall recurrence of signs and symptoms was 14% in the former group and 15.6% in the latter. There were no statistically significant differences between the 2 groups in rates of pregnancy and recurrence (p = .700 and .832, respectively). Nor was there any significant statistical difference between the same stages in the 2 groups regarding immunomodulation.

CONCLUSIONS: According to the results of this study, and while keeping in mind that appropriate surgery is the main aspect of endometriosis treatment, there is no evidence that immunomodulation with pentoxifylline aids fertility or lessens recurrence of signs and symptoms in women with different stages of endometriosis (i.e., minimal, mild, moderate, or severe).

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KEYWORDS: Pentoxifylline; Endometriosis; Endometrioma; Cumulative pregnancy rate; Infertility; Immunomodulation

It has been known for many years that endometriosis has associations with fecundity and pelvic pain. Despite many advances in diagnosis and treatment of endometriosis, it is still an enigma, and there is a great deal of controversy regarding its pathogenesis and treatment.

Although there are suggestions about involvement of an aberrant immunologic mechanism in its pathogenesis, the exact mechanism by which endometriosis interferes with fertility is not yet known. Considering immune changes,
there are alterations in the function and count of immune-related cells in the peritoneal environment. One study suggested increased number of activated macrophages in the peritoneal fluid of women with endometriosis.\(^2\) Macrophages are potent producers of cytokines, which may regulate the actions of leukocytes in the peritoneal fluid or may influence the ectopic endometrial tissue.\(^3,4\) where they may act on the pathophysiology of endometriosis and have their effect on reproductive outcome.\(^5\)

According to these facts, it sounds reasonable that manipulation of the immunity system in the peritoneal environment may be a new aspect in treating endometriosis. There is some evidence in animal models regarding the effect of pentoxifylline as an immunomodulator on endometriosis-related infertility and growth of endometriotic implants.\(^6,7\) There was also a human study of the effect of pentoxifylline on fertility in minimal and mild endometriosis, but it did not show clinical results comparable to the animal models.\(^8\)

This study is the first prospective, randomized, double blind, placebo-controlled clinical trial that compares the effects of immunomodulation of pentoxifylline with those of a placebo on treatment of infertility and resolution of signs and symptoms associated with the disease in minimal, mild, moderate, and severe endometriosis.

### Materials and methods

This study was performed from January 2002 through December 2003 in infertile patients in whom endometriosis was diagnosed by laparoscopy. This study was approved by the Shiraz University of Medical Sciences Institutional Review Board.

The patients were all infertile for at least 12 months. Some of them had symptoms such as dysmenorrhea, dyspareunia, and pelvic pain as well. They were assessed for other infertility factors by appropriate tests such as semen analysis; postcoital testing; endometrial biopsy; assessment of ovulation by basal body temperature; hormonal assay; hysterosalpingography; and finally, laparoscopy, and if needed, hysteroscopy. After exclusion of patients with other infertility factors including those with tubal obstruction, only those with different stages of endometriosis were included in this study.

All operative laparoscopies were performed by the first author with the patients under general anesthesia. A systemic laparoscopic evaluation was carried out, all of the pelvic structures and peritoneal surfaces were evaluated, and diagnosis was made by visualization of the typical endometriotic lesions or endometriomas and proven by histologic study.

Full details of the procedure were described earlier.\(^9\) In brief, lysis of the adhesions was done by sharp dissection to fully mobilize the ovaries. All areas of superficial active endometriosis involving the other ovary or the pelvic peritoneum were fulgurated. For endometriomas of 3 cm or larger in size, cystectomy was performed, with inner lining of the cysts dissected from the ovary. The samples were sent for histopathologic examination. The ovary was repaired by a Vicryl 4-0 suture. In the cysts smaller than 3 cm, fulguration and coagulation of the inner cyst wall was carried out. Endometriosis was completely eradicated at the time of surgery as far as we could tell.

Endometriosis was classified according to the revised American Fertility Society (AFS) scoring.\(^10\) Before surgery each patient was asked to record the presence and severity of pelvic pain on a 10-cm linear analog scale.\(^11\) A score of 1 to 4 was considered mild pain and was not included in this study because of similarities between pain caused by endometriosis and nonendometriotic pain in this score. A score of 5 to 7 showed moderate pain and 8 to 10 severe pain. There were no intraoperative or postoperative complications, and all of the patients were discharged from the hospital the day after the operation in good condition.

The patients entered the study immediately after surgery, and all of them gave written informed consent. They were assigned into 1 of 2 groups by simple random allocation. An independent pharmacist generated the allocation and assigned the patients to their groups. To do so, he gave each patient a number on the basis of the order of her being referred to him. For example, the first patient was enlisted as number 1 and the second as number 2 and so on. He then assigned the patients with odd numbers into one group and the patients with even numbers into another. He decided which group should be the intervention group and which one should be the control group by flipping a coin.

The patients in the intervention group received 400 mg oral pentoxifylline twice daily for 12 months, starting immediately after the surgery, whereas in the control group, the patients took oral placebo for the same period. The patients in both groups were followed up during these 12 months at 3-month intervals. Only those patients who completed this follow-up period were included in this study. During this period, neither the clinicians nor the patients knew who received the medication and who received the placebo. The only person who knew this was the pharmacist.

The items that were under focus were pregnancy rate and recurrence of the disease. At each visit, a gynecologic examination and endovaginal ultrasound scanning were done, and the patients were asked for symptoms. The histologic reports were reviewed to determine whether they confirmed the clinical diagnosis. The occurrence of pregnancy was recorded by the presence of fetal pole inside an intrauterine gestational sac on ultrasound scanning. Disease recurrence was defined as new cyst formation or recurrence of symptoms after having subsided. During the follow-up the patients did not receive any other medication or intervention for treating infertility and pain. Comparison of the data in the 2 groups was done by \(\chi^2\) test, Fisher’s exact test, Mann-Whitney U-test, and \(t\) test.
Results

Of 121 patients for whom endometriosis was diagnosed in laparoscopy and proven by histopathologic study, 33 patients were excluded from the study because they either had other infertility factors or incomplete follow-up. We studied 43 patients in the intervention group, who received pentoxifylline 400 mg twice daily and 45 patients in the control (placebo) group. General characteristics of the patients in each study group are shown in Table 1. There were no statistically significant differences between the groups regarding age, type of infertility (i.e., primary vs secondary), duration of infertility, prevalence of different stages of endometriosis, size of cysts, and AFS score of the disease. But there was a statistically significant difference in the preoperative prevalence of the symptoms such as pelvic pain, dysmenorrhea, and dyspareunia between the 2 groups (Table 1).

After 1 year of follow-up, cumulative pregnancy rates and recurrence of a cyst or symptoms (dysmenorrhea, pelvic pain) were statistically similar (Table 2). The 12-month overall pregnancy rate was 39.5% and 35.6% in the intervention and control groups, respectively (p = .700). Recurrence of signs and symptoms was 14% in the intervention group and 15.6% in the placebo. Therefore, there was again no significant difference between the 2 groups (p = .832).

Comparing different stages of endometriosis for recurrence and pregnancy rate, there was no significant statistical difference between the same stages in the 2 groups, regarding immunomodulation (Table 3). Mean interval between operative laparoscopy and pregnancy in patients who conceived was 5.35 months in pentoxifylline group and 5.87 months in placebo group, which showed no statistical difference (p = .586) (Table 2).

Discussion

It has been accepted that surgery is usually the major modality in the management of advanced stages of endometriosis to reduce symptoms and treat subfertility, especially when there is mechanical distortion of the pelvis and reconstruction of normal pelvic anatomy is necessary. In addition, many studies suggest laparoscopic surgery of endometriosis is superior to laparotomy in many aspects such as pelvic pain, dysmenorrhea, and dyspareunia.
as decreased cost, morbidity, and the possibility of recurrence of adhesions. Furthermore, diagnosis and treatment can be done concomitantly, and the patient is not subjected to a lengthy time frame or potential side effects of medical treatment. Surgical management of infertile women with minimal and mild endometriosis is controversial. Some studies proposed surgery had no advantages over expectant management; but others reported laparoscopic surgery of even early stages would result in higher pregnancy rates compared with expectant management. On the other hand, postoperative medical therapy with some agents such as estrogen-progesterone combinations, progesterones, antiprogestogens, danazol, and gonadotropin-releasing hormone agonists have been proposed, to eradicate the residual disease. They have been reported to decrease pain symptoms and recurrence of disease. However, because these drugs may interfere with ovulation during the postoperative days that are critical for conception, their use for treating infertility has been a matter of controversy. Because endometriosis has a tendency toward recurrence after surgery or medical therapy, new options that do not interfere with ovulation but have the potential to eradicate the residual disease should be considered.

According to many investigators, there are increasing data regarding the role of the immune system in the pathogenesis of endometriosis. Some of the suggested factors are defective immunosurveillance, resistance of endometrial cells to apoptosis and phagocytosis, and decreased natural killer cell activity and cytotoxicity against endometrial cells in endometriosis. Therefore the idea of using an anti-inflammatory drug to control or eradicate clinical signs and symptoms of endometriosis seems logical. These drugs include tumor necrosis factor (TNF)-α binding protein, recombinant interferon-α2B, laxorbine, and leukotriene receptor antagonists.

Pentoxifylline, a methylxanthine acting as phosphodiesterase inhibitor, is one of the antiinflammatory agents that have been proposed for treating endometriosis. The drug has been used over many years in the management of cerebrovascular and peripheral vascular diseases and other conditions with defective microcirculation. Pentoxifylline has also been shown to enhance sperm motility and the outcome of in vitro fertilization in male factor infertility. It reduces production and action of cytokines such as TNF-α, by elevation of intracellular cyclic adenosine monophosphate levels.

In surgically-induced endometriosis in rodent models, periovulatory pentoxifylline showed some benefit regarding the fertilization rate. The authors of this study suggested that periovulatory pentoxifylline could significantly reverse the effect of intraperitoneal transfer of hyperactivated macrophages, but not basal state macrophages, on fertilization in an in vivo model. There is only 1 study on the effect of pentoxifylline on fertility of human beings, in mild and minimal endometriosis. In spite of the results obtained from animal models, there is no good evidence from this study that immunomodulation with pentoxifylline improves fertility in humans.

We had a total of 88 patients with different stages of endometriosis in the control and intervention groups, which were similar regarding the stage of the disease (p = .965). The overall pregnancy rates in the intervention and control groups were 39.5% and 35.6%, respectively, which had no statistical difference (p = .700). Balasch et al reported 31% and 18.5% in the intervention and control groups, respectively, which had no statistical difference either. They studied only the patients with stages I and II, but we had the patients in all stages from I to IV.

In the previous study, there was no comparison between intervention and placebo groups about recurrence rate of signs and symptoms; however, we compared the overall recurrence rate between these groups: 15.6% in the control group and 14% in the treatment one; which again revealed no statistical difference (p = .832).

Stage-specific recurrence and pregnancy rates between the 2 groups were not evaluated in the previous study. These rates were compared in this study and showed no statistical difference. However, because of the limited number of patients in each stage, this conclusion is not supported by a high enough statistical power (Table 3).

Another point that is worth mentioning is that most of our patients were at high stages of endometriosis, and this might have affected the results of our study. So one should
not rule out the possibility that the drug might be useful in lower stages of the disease.

Conclusion

Presence of immune changes in endometriosis has long been established, as mentioned previously. Therefore, immunomodulation may be a novel method for treating endometriosis, and this is suggested by animal studies. However, in our study, we were not able to show any improvement in treatment of infertility or resolution of signs and symptoms in our study, we were not able to show any improvement in treatment of infertility or resolution of signs and symptoms by administration of pentoxifylline. Nevertheless, additional multicenter studies with a much larger number of patients are required for us to be able to reach a final verdict on the effects of immunomodulation on treatment of endometriosis.

References