Ornidazole Reduces the Progression of Endometriosis in a Rat Model

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**Abstract**

**Objective:** The aim of this study was to investigate the effectiveness of ornidazole in inhibiting the progression of endometriosis in a rat model. **Design:** This was an in vivo experiment, including the ornidazole group (\(n=16\)) and a control group (\(n=14\)). Rats were provided with free access to water containing ornidazole (1 g/L) or drinking water only for 14 days. **Materials and Methods:** Surgical induction of endometriosis was performed in Sprague Dawley rats via autologous endometrial transplantation. Rats were provided with free access to water containing ornidazole (1 g/L) or drinking water only for 14 days. Once the rats were euthanized (ornidazole group, \(n=16\); control group, \(n=14\)), histological signatures and the volumes of endometriosis lesions were assessed. Cells positive for the inflammatory cytokines interleukin (IL)-1\(\beta\), IL-6, and tumor necrosis factor (TNF)-\(\alpha\) were counted. Angiogenesis was identified by assessing vascular endothelial growth factor (VEGF) and microvessel density. **Results:** The median lesion volume was lower in the ornidazole group (20.2 mm\(^3\); range, 5.7–53.3 mm\(^3\)) than in the control group (81.3 mm\(^3\); range, 32.8–122.2 mm\(^3\); \(p=0.007\)). Median IL-1\(\beta\) cell counts were 5.3 (range, 4.5–6.4) for ornidazole and 11.7 (range, 9.4–15.4) for control (\(p<0.001\)). Mean IL-6 cell counts were 5.6 ± 1.8 for ornidazole and 11.3 ± 4.1 for control (\(p<0.001\)). Median TNF-\(\alpha\) cell counts were 5.7 (range, 4.5–7.2) for ornidazole and 12.1 (range, 10.0–15.9) for control (\(p<0.001\)). Median VEGF cell counts were 8.1 (range, 6.5–11.4) for ornidazole and 18.3 (range, 14.2–21.0) for control (\(p=0.001\)). Median microvessel density values were 11.3/HPF (range, 7.7–21.8) for ornidazole and 28.7/HPF (range, 13.1–48.2) for control (\(p=0.012\)). **Limitations:** This study is a short period and small sample size experiment. In this study, multiple drug concentrations were not used. We did not use in vitro models to assess the anti-inflammatory and antiangiogenic effects of ornidazole on endometriosis, and the specific anti-inflammatory and antiangiogenic mechanisms associated with ornidazole need to be further investigated. **Conclusion:** Ornidazole restricts the growth of endometriosis in rats, possibly by exerting anti-inflammatory and antiangiogenic effects.

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**Keywords**

Endometriosis · Ornidazole · Inflammation · Antiangiogenesis

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**Introduction**

Endometriosis is a chronic inflammatory disease that occurs mostly in women of reproductive age. This disease, which causes pain in the pelvis and lower abdomen, is characterized by the presence of endometrial-like tissue, including stromal cells and glandular epithelial cells, in the abdominal cavity [1]. The pathogenesis of endometriosis has not been fully elucidated. However, research has demonstrated that the development of endometriosis lesions is dependent on the presence of an adequate blood supply [2, 3]; Thus, to survive outside the uterine cavity, endometriosis lesions require the development of a new blood vessel network [4]. Chronic inflammatory response is also closely related to the occurrence, development, and recurrence of endometriosis [5–7]. Previous studies have therefore assessed inflammation and angiogenesis as prospective targets in the clinical treatment of endometriosis [8–10].

Ornidazole is a third-generation nitroimidazole antibiotic that is frequently used in gynecology because of its strong anti-inflammatory effect and its fewer side effects. The structural nitro may be converted into more active amines that damage microbial DNA to achieve antimicrobial action and thus play an anti-inflammatory role [11]. It is widely used in treatment of pelvic inflammatory disease, adnexitis, endometritis, and partial vaginitis. Previous studies have also shown that analogs of ornidazole demonstrate angiogenesis, anticancer properties [4, 12, 13]. Because inflammation and angiogenesis play key roles in the pathophysiology of endometriosis and because endometriosis, like cancer, is characterized by cell invasion [10, 14], we hypothesized that ornidazole may demonstrate some benefit in inhibiting the progression of endometriosis. In this study, we therefore sought to assess the effectiveness of ornidazole in inhibiting endometriosis progression in a rat model.

**Materials and Methods**

**Animal Model Used to Assess Ornidazole Treatment of Endometriosis**

This study was approved by the Ethics Committee of the Second People’s Hospital of Changzhou Affiliated to Nanjing Medical University. In 37 female Sprague Dawley rats (weight, 100–140 g; age 6–8 weeks), endometriosis was surgically induced using a well-established method described previously by the same researcher [15]. In brief, 10% chloral hydrate was injected into the abdomen of the rat for anesthesia, and the abdomen was then opened. Both ends of one uterine horn were ligated. A 1-cm segment of the uterus was split longitudinally and divided into 4 segments, and these segments were stitched separately to the upper and lower and left and right quadrants near the abdominal incision. The abdominal cavity was then closed.

The next day, the animals were randomly divided into 2 groups: the ornidazole group, in which animals received water containing ornidazole (1 g/L; Shandong Lukang Pharmaceutical Group, Shandong, China), and the control group, in which animals received equivalent drinking water. Both groups were provided with constant access to this water for 14 consecutive days [16]. The animals were then euthanized via cervical dislocation, and the abdominal cavity was opened along the original incision so that the length, width, and height of the explants could be measured using calipers. Macroscopically visible lesions were recorded in detail with respect to localization, phenotype (cystic or solid appearance), and number. The volume of the explant was calculated by multiplying the mean of the sum of the 4-quadrant volumes by 0.52 [17, 18]. The lesions were then removed and soaked in 10% formalin liquid.

**Histological and Morphological Analysis**

The tissues were fixed with 10% paraformaldehyde, and the paraffin-embedded specimens were then cut into 4-μm sections. Segments of these sections were used for histochemical staining with hematoxylin and eosin. Once staining was complete, the specimens were examined with a microscope to identify the histological characteristics of endometriosis such as the presence of endometrial-like glands and stroma.

**Immunohistochemistry Staining**

The other paraffin-embedded specimens were used for immunohistochemistry staining with streptavidin-biotin complex. Subsequent to dewaxing and rehydration, the tissue sections are placed in a repair box filled with citric acid (pH 6.0) antigen retrieval buffer for antigen retrieval in a microwave oven. The sections are placed in 3% hydrogen peroxide in order to block endogenous peroxidase activity, incubated with normal goat serum, and the tissues are sealed for 30 min at 37°C. IL-1β (1:800; GB11113; Servicebio, Wuhan, China), IL-6 (1:800; GB11117; Servicebio, Wuhan, China), TNF-α (1:200; GB11188, Servicebio, Wuhan, China), VEGF (1:100; Ab52917; Abcam, Cambridge, USA), and CD34 (1:100; M7165; Dako, Denmark) were incubated with the sections at 4°C overnight. The sections are placed in PBS (pH 7.4) and washed by shaking, then covered with antibody (HRP labeled) from the corresponding species of primary antibody and incubated at 37°C for 50 min. Newly prepared DAB color developing solution is added after the sections are slightly dried. The sections were counterstained with hematoxylin stain solution, differentiated with hematoxylin differentiation solution, and treated with hematoxylin returning blue solution. After dehydration and mounting, staining of the tissue was visualized under a microscope.

For analysis of cytokine density (including the cytokines IL-1β, IL-6, TNF-α, and VEGF), the slides were evaluated at a magnification of ×100, and 5 areas with high densities of cytokine marker accumulation (brown) were identified. The 5 areas were then counted at a magnification of ×400, and the mean positive cell value was determined for each segment. For analysis of microvessel density, rabbit anti-mouse CD34 polyclonal antibody staining was used to identify positive cells, which appeared as brown. Using Weidner’s microvessel density counting method, we selected very dense areas of microvessel at a magnification of ×100 and then
counted microvessel density on 5–10 views at a magnification of ×400 [19]. The mean of the 3 maximum values was then selected as the microvessel density value for each case individually. All protocols were performed by one researcher who was blinded to the groups, with assistance provided by a professional pathologist.

**Statistical Analysis**

SPSS 25.0 software was used for statistical analysis. For continuous variables with normal distribution, analysis was performed using an independent-samples t test, and the data were expressed as mean ± standard deviation. For continuous variables with nonnormal distribution, a nonparametric test with 2 independent samples (Mann-Whitney U test) was used for analysis, and the data were expressed as median (p_{25}, p_{75}). p values <0.05 were used to indicate statistically significant difference.

**Results**

**Ornidazole Inhibited the Growth of Endometriosis Lesions**

Of the 37 rats, 3 died from anesthesia accidents and 3 died from bites from other rats on days 1, 2, and 8 (1 from treatment group and 2 from control group). Finally, 31 rats survived and did well till the end of the study. Among the surviving rats, 1 in the control group had no obvious lesions; vesicular structures of various sizes could be seen in the remaining 30 rats (ornidazole group, 16 rats; control group, 14 rats).

After 14 days of treatment, the endometriosis lesions were smaller in the ornidazole group than in the control group, and hematoxylin and eosin staining demonstrated atrophy of the endometrium, thinning of the epithelial layer, and decrease in glandular tissue in the ornidazole group (shown in Fig. 1). The median volume of endometriosis lesions in the ornidazole group (20.2 mm³; range, 5.7–53.3 mm³) was significantly smaller than the volume in the control group (n = 14) and in the ornidazole group (n = 16). Bar represents p_{25}, p_{75}. **p < 0.01.

![Fig. 1. Images demonstrated gross specimen morphology in a rat from the control group (a) and in a rat from the ornidazole group (b) after 14 days of treatment. Corresponding images demonstrate histomorphology after H&E staining in a rat from the control group (c) and in a rat from the ornidazole group (d). The volume of cystic lesions in the ornidazole group was smaller than the volume in the control group (the white arrow). Note that the epithelial layer became thinner and the glandular tissue was decreased in the ornidazole group (the black arrow). H&E, hematoxylin and eosin.](image)

![Fig. 2. Median volume of ectopic endometrial lesions in the control group (n = 14) and in the ornidazole group (n = 16). Bar represents p_{25}, p_{75}. **p < 0.01.](image)
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There was no significant difference between the groups in the expression of the cytokines of IL-1β, IL-6, or TNF-α in the epithelium. However, the levels of these cytokines in the stroma were significantly lower in the ornidazole group than in the control group (shown in Table 1).

Ornidazole Inhibited the Inflammatory Reaction in Endometriosis Lesions

There was no significant difference between the groups in the expression of the cytokines of IL-1β, IL-6, or TNF-α in the epithelium. However, the levels of these cytokines in the stroma were significantly lower in the ornidazole group than in the control group (shown in Fig. 2). The median positive cell values for IL-1β were 5.3 (range, 4.5–6.4) in the ornidazole group and 11.7 (range, 9.4–15.4) in the control group ($p < 0.001$). The mean positive cell values for IL-6 were $5.6 \pm 1.8$ in the ornidazole group and $11.3 \pm 4.1$ in the control group ($p < 0.001$). The median positive cell values for TNF-α were 5.7 (range, 4.5–7.2) in the ornidazole group and 12.1 (range, 10.1–15.9) in the control group ($p < 0.001$) (shown in Table 1).

Fig. 3. Images demonstrate ectopic lesions stained for IL-1β (a, d), IL-6 (b, e), TNF-α (c, f) at a magnification of ×400. The number of cells positive (brown) for IL-1β, IL-6, and TNF-α in the stroma was significantly lower in the ornidazole group (a–c, respectively) than in the control group (d–f, respectively).

Fig. 4. Inflammatory cytokines in the stroma were significantly lower in the ornidazole group ($n = 16$) than in the control group ($n = 14$). Data are presented as mean or median, with bars representing SD or $p_{25}, p_{75}$. ***$p < 0.001$. SD, standard deviation.
Ornidazole Inhibited the Process of Angiogenesis in Endometriosis Lesions

Ornidazole treatment significantly decreased the neovascularization of endometriosis lesions (shown in Fig. 5). The median microvessel density was 11.3/HPF (range, 7.7–21.8) in the ornidazole group and 28.7/HPF (range, 13.2–48.2) in the control group ($p = 0.012$) (shown in Fig. 6). In addition, the median positive cell values for VEGF in the stroma in were significantly lower in the ornidazole group (8.1; range, 6.5–11.4) than in the control group (18.3; range, 14.2–21.1; $p = 0.001$) (shown in Table 1; Fig. 7, 8).

Discussion

In this study, we found that treatment with ornidazole restricted the growth of endometriosis in a rat model, perhaps by exhibiting anti-inflammatory and antiangiogenic effects. The endometriosis lesions were smaller in the ornidazole group than in the control group, and both microvessel density and the expression of IL-1β, IL-6, TNF-α, and VEGF in endometriosis lesions were decreased in rats that received ornidazole.

Endometriosis is a chronic inflammatory disease that is associated with local and systemic elevations in inflam-
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Inflammatory cytokines and chemokines [20]. Although endometriosis lesions are considered benign, they are similar in many ways to tumors, like neoangiogenesis [14]. The balance between proangiogenic and antiangiogenic factors and between pro-inflammatory and anti-inflammatory factors thus determines the extent of lesion progression [21], which has led researchers to investigate the use of anti-inflammatory and antiangiogenic drugs for this condition. In this study, we found that ornidazole suppressed both inflammation and angiogenesis in endometriosis lesions, inhibiting the progression of endometriosis and resulting in reduced lesion size.

The hypothesis that there is a relationship between inflammation and endometriosis is well known. In an inflammatory response, the recruitment of inflammatory cells is increased, and subsequent acute inflammation involves the local vascular system, somatic cells, and immune cells. The levels of inflammatory cytokines and growth factors are increased; these factors may promote the attachment, invasion, and proliferation of endometriosis cells. Previous studies have demonstrated that macrophages are increased in the systemic circulation of patients with endometriosis [22, 23]. Macrophages demonstrate selective anti-inflammatory and profibrotic activities and are able to induce both immunotolerance and angiogenesis [24], functions that are associated with the secretion of cytokines such as IL-1β, IL-6, and TNF-α. These findings again suggest that addressing the immune response is a key factor in treating inflammatory disorders such as endometriosis. In this study, the median positive cell values of IL-1β, IL-6, and TNF-α in the ornidazole group were significantly lower than in the control group, suggesting that ornidazole has an anti-inflammatory effect in endometriosis.

We also assessed the effect of ornidazole on the vascularization of endometriosis lesions and found that rats in the ornidazole group had significantly lower VEGF and microvessel density values than those in the control group, suggesting that ornidazole has an anti-inflammatory effect in endometriosis.

![Figure 6](image1.png) **Fig. 6.** Median microvessel density in the ornidazole group (n = 16) was significantly lower than in the control group (n = 14). Bars represent p25, p75. *p < 0.05.

![Figure 7](image2.png) **Fig. 7.** Images demonstrate immunohistochemical staining of samples from the control group (a) and from the ornidazole group (b) at a magnification of ×400. Compared with the control samples, the ornidazole samples demonstrated significantly fewer VEGF-positive in the stroma, with almost only positive cells in the blood vessels (brown).

![Figure 8](image3.png) **Fig. 8.** VEGF levels in the stroma were significantly lower in the ornidazole group (n = 16) than in the control group (n = 14). Data are presented as mean ± SD or as median (p25, p75). ***p < 0.001.
research has demonstrated that this factor is associated with angiogenesis in endometriosis [25]. Blood vessels could be observed grossly in cases of large endometriomas, which emphasizes the important role of angiogenesis in endometriosis growth [26]. Because angiogenesis is necessary for the development of endometriosis, drugs that target vascularization are potential prospects for treatment [21]. Our results suggest that ornidazole may be one such potential prospect.

This study had several limitations. First, the sample size in this study was small. Second, multiple drug concentrations were not used in this study. Third, the study period was short. Because endometriosis is a chronic inflammatory disease, cytokine levels may vary over time, and so further studies with longer treatment and follow-up periods are needed. Fourth, our findings are from a rat model of surgically induced endometriosis, and we did not evaluate the optimal dose of ornidazole or its hepatotoxicity and nephrotoxicity in rats. Further research is needed to assess the safety and efficacy of ornidazole. Finally, we did not use in vitro models to assess the anti-inflammatory and antiangiogenic effects of ornidazole on endometriosis. For the relationship between antibiotics and endometriosis, Machado et al. [27] demonstrated that clotrimazole interferes with the estrogen production pathway; thus, the drug decreases endometriotic lesion size and consequently disease progression. Chadchan et al. [16] thought that antibiotic therapy reduces endometriosis progression in mice, possibly by reducing specific gut bacteria. However, the specific anti-inflammatory and antiangiogenic mechanisms associated with ornidazole need to be further investigated in more relevant and larger animal models before these findings can be translated to clinical research.

In conclusion, our results demonstrated that treatment with ornidazole restricts the growth of endometriosis in a rat model, likely by suppressing inflammation and angiogenesis. These preliminary findings may be considered a step forward in the understanding of endometriosis treatment. Further studies are needed to assess the potential of ornidazole as a new treatment option for endometriosis.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Second People’s Hospital of Changzhou Affiliated to Nanjing Medical University, approval number (2021) KY001-01.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by Xiaoduo Qin, Haiyan Yang, Dan Qiao, Su-Fen Liu, Xuantong Liu, and Li-Bing Liu. The first draft of the manuscript was written by Xiaoduo Qin, Zhongzhi Jia put forward the main revision suggestion to the article, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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