Review / Derleme

DOI: 10.4274/tjod.galenos.2024.82610

Turk J Obstet Gynecol 2024;21:118-22

Effects of bazedoxifene on endometriosis in experimental animal models: A systematic review and meta-analysis

Deneysel hayvan modellerinde bazedoksifenin endometriozis üzerine etkileri: Sistematik bir derleme ve meta-analiz

Reza Hassanzadeh Makoui[1], Shiva Fekri[2], Negar Ansari[3], Masoud Hassanzadeh Makoui[4]

[1]*Zanjan University Faculty of Medicine, Department of Immunology, Zanjan, Iran*
[2]*Zanjan University Faculty of Medicine, Department of Obstetrics and Gynecology, Zanjan, Iran*
[3]*Zanjan University Faculty of Medicine, Department of Internal Medicine, Zanjan, Iran*
[4]*Zanjan University Faculty of Medicine, Department of Immunology, Zanjan, Iran*

Abstract

Endometriosis is a prevalent condition in women that causes pelvic pain and fertility issues due to the growth of endometrial tissue outside the uterus during menstrual cycles. Steroid hormones play a crucial role in the development and growth of endometriosis lesions; therefore, researchers have investigated several effective drugs that target hormones for treating this disease. One such drug is bazedoxifene, but despite several animal studies, there has yet to be a comprehensive evaluation of their combined results. A systematic search was conducted across several databases (Embase, PubMed, Scopus, and Web of Sciences) to identify studies investigating the effectiveness of bazedoxifene in animal models of endometriosis. Meta-analysis was performed using the size of endometriosis implants before and after drug administration in the case and control groups, along with the p-value of the associations. Begg's and Egger's tests were used to assess publication bias. This study included four eligible studies consisting of 45 endometrial animal models and 35 control subjects. The meta-analysis showed that bazedoxifene significantly reduced the size of endometriosis implants in animal models compared with the control group (odds ratio: 0.122, 95% confidence interval: 0.050-0.298, p<0.001). Detailed investigation determined that there was no significant heterogeneity between the studies (I^2=38.81, and p-value of the Q test=0.179). However, according to Egger's test, the study showed publication bias (p=0.035). This study found that bazedoxifene is a promising treatment option for endometriosis in animal models. However, more research on animals and humans is required to confirm these results.

Keywords: Animal model, bazedoxifene, endometriosis, meta-analysis

Öz

Endometriozis, adet döngüleri sırasında uterus dışında endometrial dokunun büyümesi nedeniyle kadınlarda yaygın bir durumdur ve pelvik ağrı ve doğurganlık sorunlarına neden olur. Steroid hormonlar, endometriozis lezyonlarının gelişiminde ve büyümesinde önemli bir rol oynadığından, araştırmacılar bu hastalığın tedavisinde hormonlara hedef olan birçok etkili ilacı araştırmışlardır. Bazedoksifen gibi bir ilaç da bunlardan biridir, ancak birkaç hayvan çalışmasına rağmen, bunların birleşik sonuçlarının kapsamlı bir değerlendirmesi henüz yapılmamıştır. Endometriozis hayvan modellerinde bazedoksifenin etkinliğini araştıran çalışmaları belirlemek için Embase, PubMed, Scopus ve Web of Sciences gibi birkaç veritabanında sistemik bir arama yapıldı. Meta-analiz, olgu ve kontrol gruplarında ilaç uygulamasından önce ve sonra endometriozis implantlarının boyutunu, ilişkilerin p-değeri ile birlikte kullanarak gerçekleştirildi. Yayın yanlılığını değerlendirmek için Begg ve Egger testleri kullanıldı. Bu araştırma, 45 endometrial hayvan modeli ve 35 kontrol grubundan oluşan dört uygun çalışmayı içermektedir. Meta-analiz, bazedoksifenin endometriozis implantlarının boyutunu kontrol grubuna kıyasla önemli ölçüde azalttığını göstermektedir (risk oranı: 0,122, %95 güven aralığı: 0,050-0,298, p<0,001). Detaylı inceleme, çalışmalar arasında anlamlı bir heterojenlik olmadığını belirlemiştir (I^2=38,81 ve Q testinin p-değeri=0,179). Ancak, Egger'ın testine göre, çalışma yayın yanlılığı göstermiştir (p=0,035).

PRECIS: An investigation was conducted to analyze the effects of bazedoxifene on endometriosis animal models by a comprehensive review of the existing literature.

Address for Correspondence/Yazışma Adresi: Asst. Prof. Masoud Hassanzadeh Makoui, MD,
Zanjan University Faculty of Medicine, Department of Immunology, Zanjan, Iran
Phone: +98 243 345 12 19 **E-mail:** dr.m.makoui@zums.ac.ir **ORCID ID:** orcid.org/0000-0001-6673-6692
Received/Geliş Tarihi: 04.03.2024 **Accepted/Kabul Tarihi:** 15.04.2024

Bu çalışma, bazedoksifenin endometriozis için hayvan modellerinde umut verici bir tedavi seçeneği olduğunu bulmuştur. Bununla birlikte, bu sonuçları doğrulamak için hayvanlar ve insanlar üzerinde daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Hayvan modeli, bazedoksifen, endometriozis, meta-analiz

Introduction

Endometriosis is the presence of endometrial glands and stroma-like lesions outside the uterus[1]. It is a long-lasting and debilitating condition linked to pelvic pain and infertility[2]. Approximately 10% of women in their reproductive years experience endometriosis, a condition that can be challenging to diagnose because of its complexity and diverse symptoms[3,4]. Several theories have been proposed regarding the etiology of endometriosis lesions. Some of them refer to the role of steroids and their receptors in controlling cells within abnormal endometrial lesions in endometriosis[5]. Research has revealed that ectopic endometrial tissues can produce estrogen and display variations in the expression of estrogen receptors, enzymes, and molecular pathways associated with hormones. These molecular changes play a crucial role in the formation and growth of endometriosis lesions[6].

Over time, numerous treatment choices have emerged for managing endometriosis. The primary aims of these treatments were to reduce pain and inhibit hormonally active endometriotic tissue[7]. These options encompass nonsteroidal anti-inflammatory drugs and various hormonal therapies such as combined oral contraceptives, progesterone-only contraceptives, gonadotropin-releasing hormone agonists, aromatase inhibitors, and danazol[8]. Although these therapies have shown considerable success, they come with undesired side effects due to hormonal suppression and require vigilant monitoring[8,9]. One of the newly proposed hormone-effective drugs for treating endometriosis is bazedoxifene[7].

Bazedoxifene, a third-generation selective estrogen receptor modulator (SERM), is used in combination with conjugated estrogens to treat vasomotor symptoms related to menopause and prevent postmenopausal osteoporosis[10]. SERMs have a unique ability to function as both activators and inhibitors. They can activate estrogenic effects in specific tissues, such as the bone and liver, while inhibiting estrogenic actions in other areas, like the uterus and breast[11]. Bazedoxifene did not stimulate the endometrium in clinical trials, indicating its exceptional endometrial safety[12].

Various studies have explored the impact of bazedoxifene on endometriosis in animal models, but the findings of these studies have yet to be compiled and analyzed in a comprehensive study. Therefore, we have decided to systematically analyze animal studies in this research to better understand the effect of bazedoxifene on endometriosis.

Materials and Methods

Search Strategy

Studies were identified through a comprehensive literature search of Embase, PubMed, Scopus, and Web of Sciences (up to February 16, 2024) using the keywords "Endometriosis" and "Bazedoxifene" along with their respective synonyms. Furthermore, the reference lists of the articles that were retrieved were manually examined to discover any other pertinent studies. There were no language restrictions imposed.

Study Selection and Data Extraction

The research papers were evaluated by two reviewers (RHM and NA), and only those that met the inclusion and exclusion criteria were selected. In cases of disagreement, a third- party (SF) was consulted for resolution. Our main inclusion criteria were case-control studies that investigated the effect of bazedoxifene on endometriosis in animal models. In our study, the following exclusion criteria were employed: 1) research without a control group; 2) studies conducted on humans or *in vitro*; 3) letters, editorials, abstracts, conference abstracts, and publications with inadequate information. The information gathered was entered into an Excel spreadsheet that contained the surname of the first author, the study's location and date, the total number of cases, the number of controls, the race of the involved animals, the age of the cases and controls, the method of drug administration, the dosage of bazedoxifene administered, the experimental plan, the average size of endometriosis implants before and after drug administration in both case and control animals, and the calculated p-values for the associations. The key features of the selected studies are outlined in Table 1.

Assessing the Risk of Bias

Two authors (RHM and NA) assessed the quality of each case–control study using the CAMARADES 10-item quality checklist[13]. A third reviewer (SF) was assigned the responsibility of addressing any inconsistencies that may have arisen. This checklist includes criteria such as 1) publication in a peer-reviewed journal, 2) control of temperature, 3) random allocation to groups, 4) allocation concealment, 5) blinded assessment of outcome, 6) use of an anesthetic without intrinsic neuroprotective activity, 7) use of comorbid animals, 8) sample size calculation, 9) compliance with animal welfare regulations, and 10) a statement of potential conflicts of interest. A quality score of a maximum of 10 points was assigned to each study, and a median quality score for the included studies was then determined.

Statistical Asnalysis

The CMA 3.0 software (Biostat, USA) was used to conduct statistical analyses. Odds ratios (ORs) were calculated, along with 95% confidence intervals (CIs), to evaluate the effect of bazedoxifene on endometriosis by considering the size of the endometrial implants before and after the treatment in both the case and control groups, as well as the calculated p values. The statistical heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic. The random-effects model was used to combine the data in cases of heterogeneity, whereas the fixed-effect model was employed when there was no heterogeneity. To determine publication bias, a funnel plot was created and Egger's regression asymmetry test was applied. A sensitivity analysis was conducted to assess the dependability of the combined findings.

Ethics Statement

The purpose of this research is to analyze previously published data, and there are no ethical concerns associated with this.

Results

Study Design and Description of the Included Studies and Risk of Bias Assessment

After conducting a comprehensive literature search, 85 studies were identified. After removing duplicates, 51 titles and abstracts were reviewed. Of these, 19 studies were chosen for a thorough evaluation of their full texts. Finally, after applying the inclusion and exclusion criteria, four studies were deemed suitable for inclusion in our meta-analysis. The details of the literature screening process are shown in Figure 1. The selected studies provided information on 45 animal models with endometriosis and 35 animals in the control group. These studies have reported estimates regarding the association between the impact of bazedoxifene and endometriosis. The quality of the studies was evaluated using the CAMARADES 10-item quality checklist, as described in the methods section, and the corresponding scores are displayed in Table 1. The median quality score of the included studies was 6.5 (range 5 to 8).

Main Analysis

The studies conducted by Kulak et al.[14], Naqvi et al.[15], Sakr et al.[16], and Lyu et al.[17] revealed that the mean size of endometriosis implants in the bazodexifene treatment groups was 21, 8.8, 8.7, and 24 mm^3, whereas the control groups had mean sizes of 60, 19.6, 31, and 48 mm^3, respectively. The meta-analysis of these findings showed that bazedoxifene causes a significant reduction in the size of endometriosis implants in animal models compared with the control group (OR: 0.122, CI 95%: 0.050-0.298, p<0.001). This suggests that bazedoxifene may have valuable therapeutic properties for treating endometriosis. Figure 2 displays the relevant forest plot.

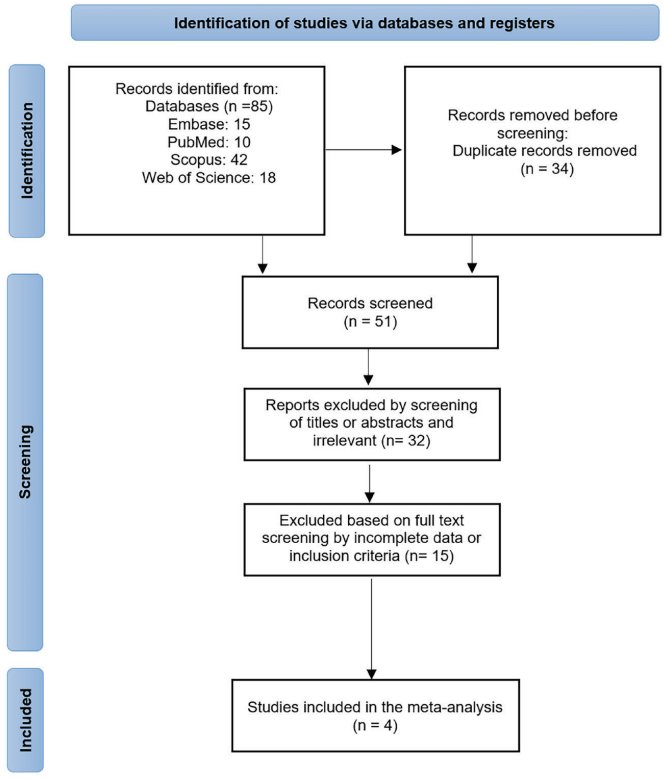

Figure 1. Flowchart for selection of studies

Table 1. Basic characteristics of the included studies

First author	Year	Country	Number of included cases	Number of included controls	Type of animal model	Age of the included animals (weeks)	Injected dose of bazedoxifene (mg/kg per day)	Rout of drug administration	CAMARADES quality assessment Score
Kulak et al.[14]	2011	USA	10	10	CD1 female mice	8	3	Intraperitoneal	6
Naqvi et al.[15]	2014	USA	20	10	CD1 female mice	8	1, 2, 3, 5	Intraperitoneal	5
Sakr et al.[16]	2014	USA	5	5	Female C57BL/6 mice	8-10	3	Intraperitoneal	8
Lyu et al.[17]	2015	China	10	10	Female rats	8-10	-	Intraperitoneal	7

Heterogeneity Analysis

Cochran's Q test and the I^2 statistic were employed to assess heterogeneity. The I-squared test resulted in a value of 38.81, and the p-value for the Q test was 0.179. Based on these findings, it can be concluded that there was no significant heterogeneity among the studies. Therefore, a fixed-effects model was used to analyze the data.

Publication Bias

A funnel plot was drawn to check for potential publication bias (Figure 3). The funnel plot of the included studies displays some asymmetry, which could be due to the small number of studies analyzed. Furthermore, while the Begg and Mazumdar rank correlation test did not show statistically significant results for publication bias (p=0.308), the Egger's test yielded significant findings (p=0.035). These findings indicate that some studies do not have been published because they did not achieve the desired outcomes.

Sensitivity Analysis

To assess the strength of the estimated combined effect size, we conducted a sensitivity analysis by systematically excluding one study at a time and reevaluating the combined effect size based on the remaining studies. The findings revealed that the combined effect remained consistent, suggesting that the outcomes were not influenced by any individual study. This outcome confirmed the validity of our findings.

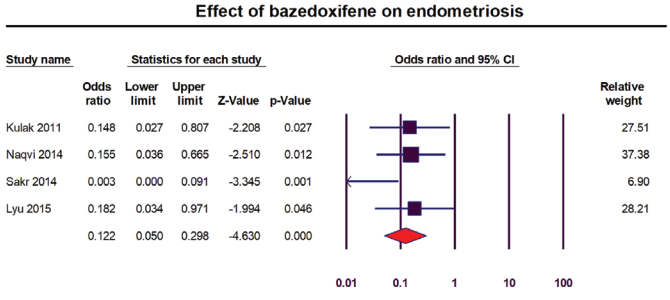

Figure 2. Meta-analysis to investigate the effect of badoxifene on the size of endometriosis graft lesions in animal models

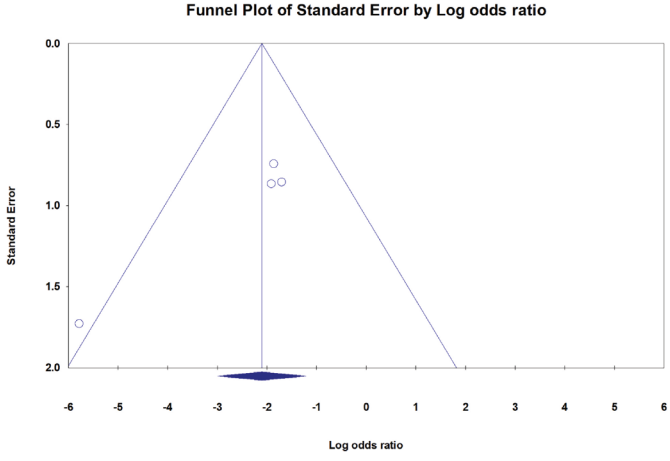

Figure 3. Begg's funnel plots for the studies that evaluated the effects of bazedoxifene on endometriosis

Discussion

Endometriosis is a complicated and common women's disease that is difficult to treat because of various factors affecting its progression[18]. Bazedoxifene is a new treatment option for endometriosis that has demonstrated promising results in animal studies and several case reports of human patients. This study aims to collect and analyze data on the effects of bazedoxifene on animal models of endometriosis.

Our study showed that the size of endometriosis implants in animals treated with bazedoxifene was significantly reduced compared with the control group. The meta-analysis results of the included studies consistent with their findings and validated their conclusions. Kulak et al.[14], Naqvi et al.[15], and Sakr et al.[16] in mice models, as well as Lyu et al.[17] in rat models, all reported that bazedoxifene can decrease the size of endometrial implants.

Some studies have attempted to uncover the underlying mechanism of action of bazedoxifene in treating endometriosis. Kulak et al.[14] found that bazedoxifene's ability to reduce estrogen-mediated cell proliferation is the reason for its effectiveness in treating endometriosis. This is evidenced by the decreased expression levels of estrogen receptor and proliferating cell nuclear antigen. Nevi et al.[15] discovered that bazedoxifene reduces the expression of estrogen receptor 1 without affecting the expression of progesterone receptors. Sakr et al.[16] reported that bazedoxifene reduced stem cell recruitment and restored endometrial engraftment. Furthermore, Hou et al.[19] showed that VEGF, VEGFR2, and COX-2 expression levels were significantly lower in endometriosis animal models treated with bazedoxifene than in the untreated control group. This suggests that bazedoxifene effectively reduces the vascularization and expansion of endometriosis lesions.

Limited studies have investigated the effects of bazedoxifene on endometriosis in humans. Flores et al.[20] reported that a combination therapy of bazedoxifene and conjugated estrogens relieved pelvic pain in a patient with stage III endometriosis. In a separate study, Hill et al.[21] treated three patients with endometriosis who did not respond to traditional drug therapy by administering a combination of bazedoxifene, conjugated estrogens, and leuprolide. The findings of these studies align with the results obtained from our research, suggesting that bazedoxifene may reduce endometriosis lesions and stop pelvic pain and bleeding in these patients.

This study is the first systematic review and meta-analysis that specifically examines the impact of bazedoxifene on endometriosis in animal models. In addition, the studies included in this research were highly homogeneous, which enhanced the accuracy and reliability of the investigation results. Our study has some limitations that we should mention. First,

limited studies were available to conduct this research, and repeating this investigation with more available studies would be beneficial. Furthermore, the studies we analyzed in our research only focused on the effect of bazedoxifene in reducing the size of endometriosis implants in animal models. However, to determine the complete efficacy of bazedoxifene in treating endometriosis, it is essential for future studies to also evaluate its ability to alleviate other symptoms, such as pelvic pain and bleeding.

Conclusion

In summary, the findings of this research suggest that bazedoxifene shows promising clinical effectiveness in treating endometriosis in animal models, indicating its potential as a future treatment option for this condition. However, further research involving both animals and humans is imperative to validate these results.

Ethics

Authorship Contributions

Design: S.F., M.H.M., Data Collection or Processing: R.H.M., N.A., Analysis or Interpretation: S.F., R.H.M., N.A., M.H.M., Literature Search: M.H.M., Writing: S.F., R.H.M., N.A., M.H.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Parasar P, Ozcan P, Terry KL. Endometriosis: Epidemiology, Diagnosis and Clinical Management. Curr Obstet Gynecol Rep 2017;6:34-41.
2. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. The Lancet 2021;397:839-52.
3. Tore U, Abilgazym A, Asunsolo-del-Barco A, Terzic M, Yemenkhan Y, Zollanvari A, et al. Diagnosis of Endometriosis Based on Comorbidities: A Machine Learning Approach. Biomedicines 2023;11:3015.
4. Zieliński K, Drabczyk D, Kunicki M, Drzyzga D, Kloska A, Rumiński J. Evaluating the risk of endometriosis based on patients' self-assessment questionnaires. Reprod Biol Endocrinol 2023;21:102.
5. Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell 2021;184:2807-24.
6. Yland J, Mathyk B, Young LS. Steroid Hormones and Endometriosis. Current Women`s Health Rev 2018;14:117-26.
7. Shi J, Tan X, Feng G, Zhuo Y, Jiang Z, Banda S, et al. Research advances in drug therapy of endometriosis. Front Pharmacol 2023;14:1199010.
8. Rafique S, Decherney AH. Medical Management of Endometriosis. Clin Obstet Gynecol 2017;60:485-96.
9. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord 2022;23:333-55.
10. Palacios S, Mejía Ríos A. Bazedoxifene/conjugated estrogens combination for the treatment of the vasomotor symptoms associated with menopause and for prevention of osteoporosis in postmenopausal women. Drugs Today (Barc) 2015;51:107-16.
11. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. Clin Interv Aging 2014;9:1437-52.
12. Mitwally MF. Bazedoxifene: A Selective Estrogen-Receptor Modulator. Women's Health 2008;4:319-26.
13. Macleod MR, O'Collins T, Howells DW, Donnan GA. Pooling of animal experimental data reveals influence of study design and publication bias. Stroke 2004;35:1203-8.
14. Kulak J Jr, Fischer C, Komm B, Taylor HS. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology 2011;152:3226-32.
15. Naqvi H, Sakr S, Presti T, Krikun G, Komm B, Taylor HS. Treatment with bazedoxifene and conjugated estrogens results in regression of endometriosis in a murine model. Biol Reprod 2014;90:121.
16. Sakr S, Naqvi H, Komm B, Taylor HS. Endometriosis impairs bone marrow-derived stem cell recruitment to the uterus whereas bazedoxifene treatment leads to endometriosis regression and improved uterine stem cell engraftment. Endocrinology 2014;155:1489-97.
17. Lyu H, Liu Y, Dang Q, Chen H, Chen R. [Effect of bazedoxifene on endometriosis in a rat model]. Zhonghua Fu Chan Ke Za Zhi 2015;50:291-5.
18. Dai Y, Li X, Shi J, Leng J. A review of the risk factors, genetics and treatment of endometriosis in Chinese women: a comparative update. Reproductive Health 2018;15:82.
19. Hou R, Xu H, Li H. Effect of bazedoxifene on expressions of VEGF, VEGFR2, COX-2 and inflammatory factors in a rat endometriosis model. Trop J of Pharm Res 2021;18:1799-804.
20. Flores VA, Stachenfeld NS, Taylor HS. Bazedoxifene-Conjugated Estrogens for Treating Endometriosis. Obstet Gynecol 2018;132:475-7.
21. Hill AM, Lessey B, Flores VA, Taylor HS. Bazedoxifene/conjugated estrogens in combination with leuprolide for the treatment of endometriosis. Clin Case Rep 2018;6:990-4.