Archives of Gynecology and Obstetrics (2019) 299:1305–1312
https://doi.org/10.1007/s00404-019-05057-4

GENERAL GYNECOLOGY

Effects of clarithromycin on inflammatory markers and clinical manifestations in postsurgical follow-up of patients with endometriosis: a double-blinded randomized placebo-controlled clinical trial

Saeed Alborzi[1] · Tahereh Poordast[1] · Elham Askary[1] · Gita Dorniani[1]

Received: 4 July 2018 / Accepted: 18 January 2019 / Published online: 19 March 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose Studies showed anti-inflammatory and immunomodulatory effects of macrolide antibiotics such as clarithromycin in endometriosis. Therefore, the present study aims to investigate the therapeutic efficacy of clarithromycin in patients with endometriosis.

Methods This was a double-blinded randomized placebo-controlled trial conducted on endometriotic women during March 2016–2017 in Dena Hospital, Shiraz, Iran. Immediately after surgery, the patients were randomly divided into clarithromycin (real) ($n=120$) and placebo group ($n=169$). The real group received 500 mg of clarithromycin everyday for 6 months and the placebo group received the placebo. The serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), Erythrocyte sedimentation rate (ESR) and C-reactive protein as well as clinical symptoms at baseline and 3 and 6 months of post-surgery were compared within and between groups.

Results The scores of dysmenorrhea, dyschezia, dyspareunia, and non-menstrual pain significantly decreased in both real and placebo groups compared with the baseline values. However, the real group showed greater reductions compared with the placebo group ($p<0.001$). Similarly, the serum levels of CRP, TNF-α, and IL-10 decreased in both groups compared with the baseline values, but the real group showed greater reductions. Interestingly, the reductions in the clinical symptoms and serum levels did not significantly differ between the real and placebo groups. Moreover, the reductions in the studied variables showed no dependence on the time.

Conclusion Clarithromycin may be an appropriate treatment in endometriotic patients. However, the non-significant differences between the real and placebo groups necessitate further studies on the therapeutic efficacy of clarithromycin.

Keywords Endometriosis · Clarithromycin · Tumor necrosis factor-alpha · Interleukin-10 · Dysmenorrhea · Dyspareunia · Dyschezia

Introduction

Endometriosis is an enigmatic gynecological disorder, characterized by the presence of endometrial tissues including uterine, stromal, and glandular outside of the uterine cavity [1]. It affects 5–15% of the women of reproductive age worldwide and its prevalence increases with age and infertility as the incidence increases up to 30% in patients with infertility and up to 45% in patients with chronic pelvic pain [1–3]. Endometriosis can be asymptomatic or may present with severe symptoms such as chronic pelvic pain, dysmenorrhea, deep dyspareunia, and cyclic bowel or bladder symptoms, such as dyschezia, bloating, constipation, rectal bleeding, diarrhea, and hematuria [4]. It is also responsible for subfertility, infertility, and abnormal menstrual bleeding [5] as well as for up to 60–80% of chronic pelvic pain and infertility [6].

Previous studies have reported different risk factors for endometriosis including age, prolonged menses, nulli-parity, short menstrual cycles, Müllerian anomalies, early menarche and late menopause [7]. Caucasians and Asians are under

✉ Tahereh Poordast
taherehpoordast2018@gmail.com

[1] Department of gynecology and obstetrics, Shiraz University of Medical Sciences, Shiraz, Iran

higher risk than Hispanic and black races [8]. Surgery, especially laparoscopy, is the treatment of choice for advanced stages of endometriosis to reduce symptoms, but due to the possibility of recurrence after surgery as well as high risk of reduced ovarian reserve, several agents such as progesterones, antiprogestogens, estrogen–progesterone combinations, danazol, and gonadotropin-releasing hormone agonists are used postoperatively to eradicate the residual disease [9]; nevertheless, these drugs may interfere with ovulation and fertility. Therefore, the researchers are looking for the exact pathogenesis of endometriosis to find new postsurgical adjuvant treatment options. Several studies have been conducted on understanding the pathogenesis of endometriosis [2, 9–11]. Epidemiological and laboratory studies have demonstrated that estradiol and progesterone play pivotal roles in the establishment and maintenance of the disease. Endometriosis also has been associated with a reduced response to progesterone in in both eutopic and ectopic endometrium, so that the resistance to progesterone action has been attributed to the overall reduction of progesterone receptor (PGR) levels in the patients [12]. It has been reported that endometriotic tissues depend on steroids and progesterone and endometriosis is rarely seen in postmenopausal women [12]. Moreover, endometriosis is reportedly associated with a reduced response to progesterone in both the animal and human studies. Several hypotheses have been proposed for the pathogenesis of endometriosis, but the exact etiology of the disorder is not clear. Among the proposed hypotheses are shedding of endometrial cells by retrograde menstruation, lymphatic and blood drainage, and transformation of peritoneal cavity's undifferentiated cells, known as coelomic metaplasia [11]. In addition, immune system dysfunction and alteration in humoral and cell-mediated immunity have been discussed in the pathogenesis of endometriosis [13, 14] that may result in inability to recognize the presence of endometrial tissue in abnormal locations or decrease the cytotoxicity of natural killer (NK) cells to autologous endometrium [15]. The higher concentration and presentation of leukocytes and macrophages in ectopic endometrial tissue and secretion of cytokines and growth factors like tumor necrosis factor (TNF), interleukin-1, and vascular endothelial growth factor (VEGF), by these inflammatory cells is another evidence for the immunologic pathogenesis of endometriosis that will lead to inflammation and recruitment of capillaries and growth and proliferation of the implanted endometrium [16]. Another evidence supporting the hypothesis of altered immune system function in endometriosis is the association between endometriosis and other autoimmune (inflammatory) diseases, like asthma, fibromyalgia, hypothyroidism, chronic fatigue syndrome, and allergies [10, 17].

The role of immune system in determining development of endometriosis and the clinical manifestations has guided researchers to study the efficacy of anti-inflammatory treatments. Macrolides are a group of drugs, containing macrocyclic lactone ring with more than 12 elements, commonly used as antibacterial agents, especially against atypical pathogens and Gram-positive cocci. In addition to the antifungal and antibacterial effects, they have anti-inflammatory, prokinetics, and immunomodulatory effects [18]. Clarithromycin is a 14-memberd macrolide with anti-inflammatory effect that is prescribed for different inflammatory diseases, such as asthma, cystic fibrosis, bronchiectasis, and sepsis [19, 20]. Its immunomodulatory effects is reportedly similar to dexamethasone in chronic rhino sinusitis [21].

Animal studies in rat endometriosis model have shown that clarithromycin induced apoptosis, decreased the proliferation of stromal cells, and increased interleukin-10 (IL-10) [22, 23]. To our knowledge no clinical trial has been conducted to investigate the effect of clarithromycin on human endometriosis. In addition, the conducted animal studies are limited. In this study, we hypothesized that clarithromycin may be a novel treatment option for endometriosis by affecting the inflammatory markers and decreasing clinical symptoms of the disease. In this regard, the present study was designed as a double-blinded randomized placebo-controlled clinical trial to investigate the therapeutic efficacy of clarithromycin in patients with endometriosis.

Methods

This is a double-blinded randomized placebo-controlled clinical trial conducted in Dena Hospital, Shiraz, from March 2016 to 2017. All of the protocols and experimental procedures of this study were approved by the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Code: IR.sums.rec.1394.S744) which were in complete accordance with the ethical regulations of human studies set by the Helsinki Declaration (2014). The experimental procedures of the present study including the interventions, clinical assessments, and data collections were conducted in Dena Hospital, Shiraz, Iran, which is affiliated to Shiraz University of Medical Sciences, Shiraz, Iran.

The study was registered in the Iranian Registry of Clinical Trial (Code: IRCT20170925036388N2). After the enrolment of all patients and before the start of the study, researchers completely and clearly explained all objectives and protocols of the study and possible benefits and side effects of the treatments to all participants and then all of the patients filled and signed a written consent form on their participation in the study. The patients were ensured about the confidentiality and unanimous analysis of their information.

The sample size of this study was calculated using NCSS software based on alpha error of 0.05 and power of 80%. The minimum sample size was calculated as 40 and

to improve the power of the study, the study was conducted on 289 patients. Then, the patients underwent laparoscopy surgery by one professional surgeon. First, after cutting the adhesions, ureter was released and endometriosis cysts as well as all deep lesions were removed.

Immediately after surgery the patients were entered into the study based on the following inclusion criteria: women aged 20–40 years old diagnosed with endometriosis by clinical and radiographic signs, confirmed by laparoscopy. The exclusion criteria were the presence of any inflammatory or autoimmune disease, such as Lupus erythematous, inflammatory bowel disease, Crohn's disease, rheumatism, diabetes mellitus, and smoking. Then the eligible patients were randomly assigned into two groups using a simple random allocation. The real group received clarithromycin 500 mg everyday in tablet covered (Toliddarou, Iran) for 6 months and the placebo group received a placebo agent. The placebo drug was designed by an expert pharmacist with the same physical and visual characteristics (Pharmaceutical laboratory, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran).

The drugs were kept in sealed envelopes, marked by A and B, by a statistician expert, who was the only person aware of the group allocation and provided the envelopes to the researcher based on the randomization table.

Three blood samples were obtained from all the patients at baseline (before intervention), and at 3 and 6 months after the intervention. For this purpose, 5 cc cubital venous blood samples were taken from the non-dominant hand of the participants in the sitting position. The blood samples were stored at room temperature for less than 30 min and then sent to the laboratory for the measurements of serum levels of TNF-α (IBL kit, Japan), IL-10 (IBL kit, Japan), Erythrocyte sedimentation rate (ESR) (Goldstar kit, UK), and C-reactive protein (CRP) (Bionik kit, Germany). The concentrations of TNF-α, and IL-10 were measured in each serum sample using an enzyme-linked immunosorbent assay (ELISA) (eBioscience, USA). Serum levels of these inflammatory markers were considered as the primary outcomes of the study. In addition, in the same intervals (baseline, and at 3 and 6 months after intervention), all patients were asked to record the presence and severity of pelvic pain (dysmenorrhea), dyspareunia, dyschezia, and non-menstrual pain on a 10-cm linear visual analog scale (VAS) following the researcher's explaination of the rating procedures. The scores ranging 1–4 were considered mild pain, scores of 5–7 moderate pain, and scores > 8 severe pain. The pain scores were considered as the secondary outcome of the study. The patients were instructed to distinguish and score the severity of the pain for dysmenorrhea, dyspareunia, dyschezia, and non-menstrual pain using the VAS scale. The American Society of Reproductive Medicine (ASRM) classification scale was used for the assessment of the severity of endometriosis.

The patients, the researcher, and the laboratory experts taking and analyzing blood samples were blinded on the allocation and the real or placebo type of the medications.

Following the data collection process, the data were analyzed with statistical package SPSS (Version 22, Windows) using descriptive analyses, including mean ± standard deviation (mean ± SD), and percentages for frequency. The associations between pain severity and serum levels of TNF-α, IL-10, ESR, and CRP were tested in each group and between two groups using linear logistic regression. For comparison of the variables at different intervals in each groups, the Greenhouse–Geisser test was used and for the comparison between groups, the independent t-tests and Mann–Whitney *U* test were used. For all statistical analyses, the significance level was set as 0.05 (p value < 0.05).

Results

In this randomized double-blinded placebo-controlled clinical trial total of 344 patients with stages III (moderate) and IV (severe) of endometriosis were enrolled and after eligibility criteria, 307 patients were divided into two groups of clarithromycin (133) and placebo groups ($n = 174$). Total of 289 patients finished the study and entered the analyses (real 129 in the real group and 160 in the placebo group) (Fig. 1).

In the real group 116 (72.5%) participants were in stage 4, 43 (26.9%) in stage 3 and 1 (0.6%) in stage 2. Moreover, in the real group 99 (76.7%) participants were in stage 4, 29 (22.5%) in stage 3 and 1 (0.8%) in stage 2. Fisher's exact test showed no significant difference between two groups in term of staging ($p = 0.71$).

Independent *T* test showed no significant difference in the baseline values of the VAS score, the dysmenorrhea ($p = 0.99$), dyspareunia ($p = 0.72$) and non-cyclic pain ($p = 0.99$) between the two groups. Repeated measurement analysis confirmed that the intervention had no significant effect on any of the dysmenorrhea ($p = 0.75$), dyspareunia ($p = 0.33$) and non-cyclic pain ($p = 0.73$) values, whereas the effect of time was significant for all the aforementioned variables ($p < 0.001$) (Fig. 2).

Two groups were the also same in terms of EPR ($p = 0.35$), CPR ($p = 0.78$), IL10 (0.52), and TNF-α ($p = 0.25$) before the intervention (Table 1). A separate analysis was conducted to determine the significant time effects on inflammatory markers in each group as shown in Fig. 3. Our results suggest that there was no significant difference between two groups 1 month after the intervention in term of ESR level ($p = 0.16$) However, a significant difference was found in this regard after 6 months ($p = 0.004$). On the other side, the two groups showed the same trend

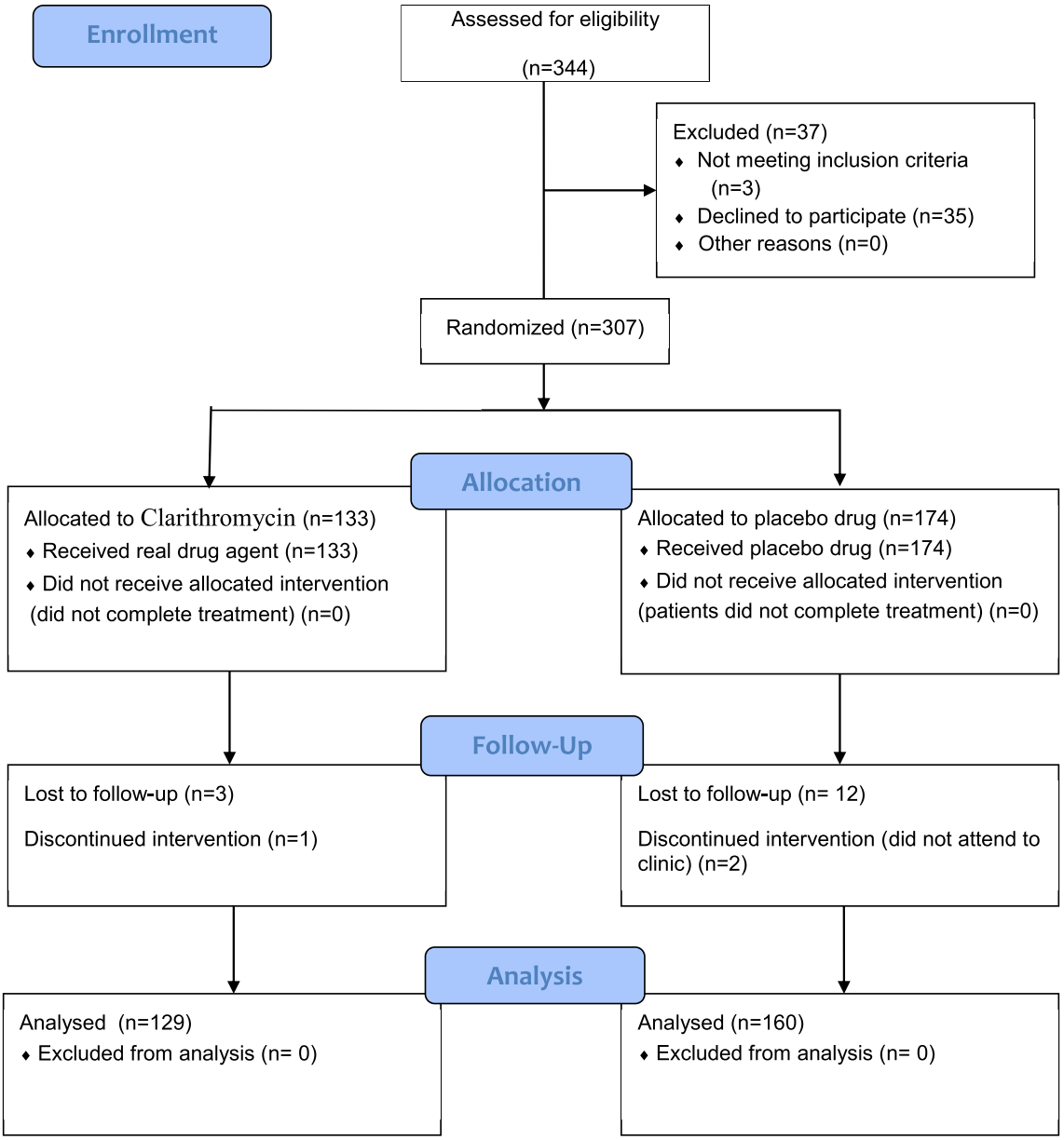

Fig. 1 The consort diagram of the study

in the CPR levels and there was no significant difference between two groups at 1 month ($p = 0.39$) and 6 months after the intervention ($p = 0.67$).

The data showed that the IL-10 and TNF-α levels were not significantly different between the real and placebo groups neither at 1 month ($p = 0.94$ and $p = 0.11$, respectively) nor at 6 months after the intervention ($p = 0.58$ and $p = 0.12$, respectively). Moreover, except for EPR and IL10 in real group ($p = 0.13$ and $p = 0.28$, respectively), effect of time was always significant in which increasing the time increased the EPR level and decreases the other aforementioned factors in both groups (Table 1).

Discussion

The present double-blinded randomized clinical trial was aimed to investigate the therapeutic efficacy of clarithromycin for the treatment of women with endometriosis. The outcomes were evaluated for 6 months following surgery and the post-intervention values were compared with the baseline values and also the variations of the variables were compared between the two groups. The results of the scores at 3 and 6 months after intervention, compared to baseline, indicated reduced clinical symptoms of

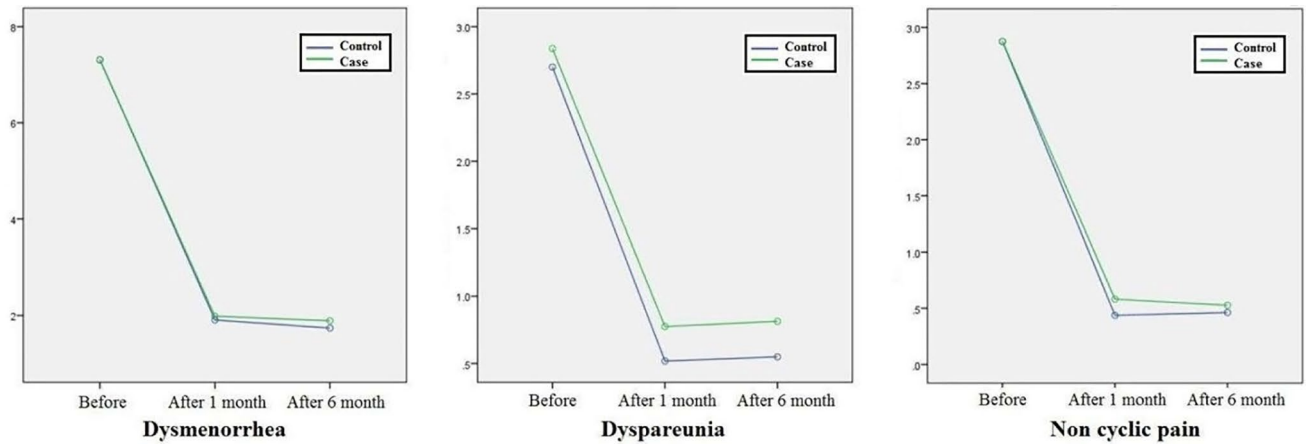

Fig. 2 Comparison of marginal means of pain between two groups

Table 1 Comparison of the mean changes in the studied factors at baseline and at 1 and 6 months after the intervention

Variable	Group	Before	After 1 month	After 6 months	Time effect *p* value
Dysmenorrhea	Real	7.3 ± 2.5	2.0 ± 2.5	1.9 ± 2.4	< 0.001
	Placebo	7.3 ± 2.4	1.9 ± 2.4	1.7 ± 2.3	< 0.001
	Between-group *p* value	0.99	0.79	0.58	–
Dyspareunia	Real	2.8 ± 3.4	0.8 ± 1.6	0.8 ± 1.7	< 0.001
	Placebo	2.7 ± 3.1	0.5 ± 1.5	0.6 ± 1.5	< 0.001
	Between-group *p* value	0.72	0.16	0.17	–
Non-cyclic pain	Real	2.9 ± 3.3	0.6 ± 1.4	0.5 ± 1.4	< 0.001
	Placebo	2.9 ± 3.4	0.4 ± 1.4	0.5 ± 1.4	< 0.001
	Between-group *p* value	0.99	0.39	0.70	–
ESR	Real	17.8 ± 12.8	20.0 ± 10.6	17.6 ± 12.0	0.13
	Placebo	16.4 ± 12.5	21.7 ± 10.2	21.5 ± 10.8	< 0.001
	Between-group *p* value	0.35	0.16	0.004	–
CPR	Real	5.9 ± 10.5	3.5 ± 2.9	3.6 ± 4.5	0.01
	Placebo	6.3 ± 12.4	4.0 ± 5.1	3.9 ± 6.3	0.01
	Between-group *p* value	0.78	0.39	0.67	–
IL10	Real	1.7 ± 3.9	1.3 ± 3.2	1.1 ± 2.9	0.28
	Placebo	2.0 ± 4.3	1.3 ± 2.8	0.9 ± 2.6	0.01
	Between-group *p* value	0.52	0.94	0.58	–
TNF-α	Real	1.1 ± 1.9	0.8 ± 1.6	0.4 ± 0.8	0.001
	Placebo	1.4 ± 2.6	0.6 ± 1.3	0.3 ± 0.6	< 0.001
	Between-group *p* value	0.25	0.11	0.12	–

endometriosis, including dysmenorrhea, dyspareunia, dyschezia, non-cyclic pain, as well as serum levels of inflammatory markers, including IL-10, TNF-α, and CRP, in both groups with significantly greater decrease in the real group (receiving clarithromycin) than the placebo group, while IL-10 was higher in the real group and TNF-α and CRP were higher in the placebo group. ESR levels increased over time in both groups, while it was higher in the placebo than the real group. To the best knowledge of the authors, this is the first study to investigate the efficacy of clarithromycin in human endometriosis and animal studies have proven that clarithromycin could regress endometrial residues in rat models [22, 23]. Additionally, light and electron microscopic evaluation reported decreased stromal proliferation and increased apoptosis of fibroblasts in rat endometriosis after clarithromycin [24]. In addition to regression of endometriosis lesions after clarithromycin, other researchers also indicated enhanced anti-inflammatory cytokine, IL-10, in rat endometriosis model [22]. The results of the present study are in line with previous animal

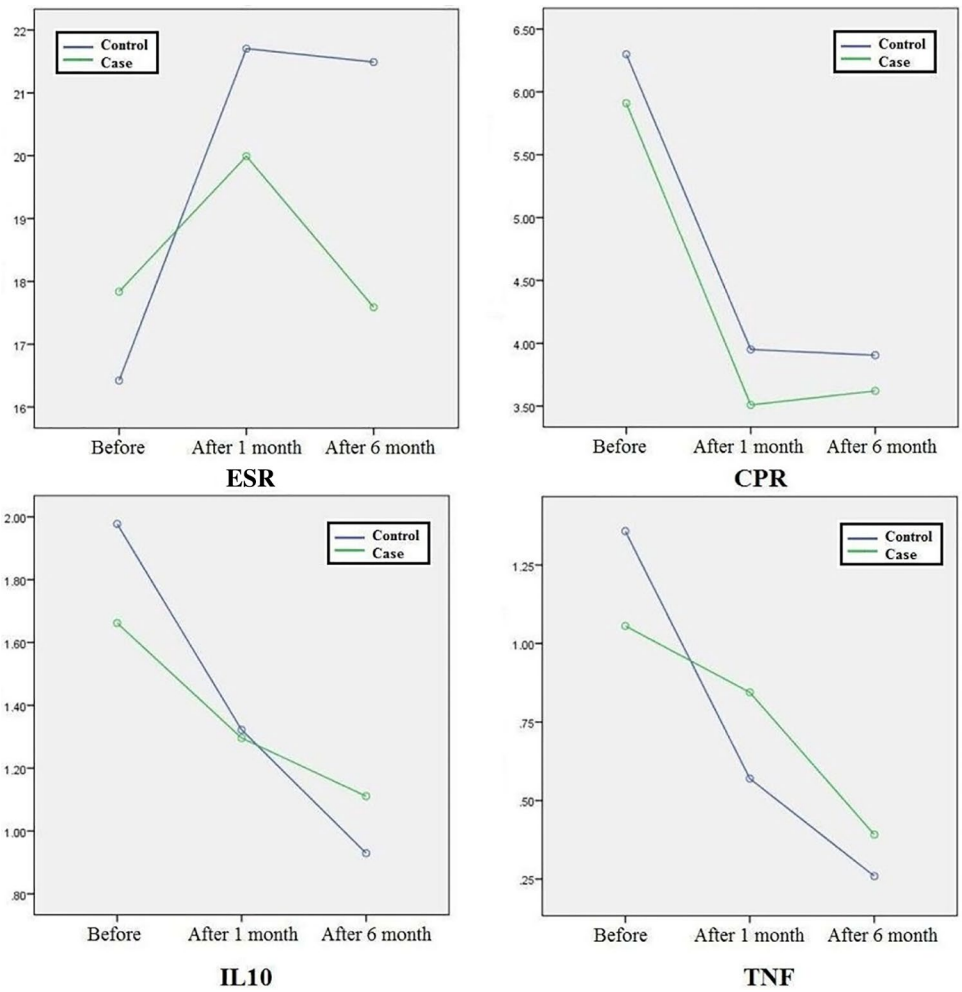

Fig. 3 Comparison of marginal means of inflammatory markers between two groups

studies in general, while surgical evaluation of patients after the treatment was not ethical in humans to observe the regression of endometriosis, although reduced symptoms in the present study suggest regression of endometriosis, consistent with the results of previous animal studies.

In our study, we followed patients for 6 months to observe the changes in clinical symptoms (dyspareunia, dyschezia, and dysmenorrhea) and inflammatory markers and the results revealed that the clinical symptoms decreased in both groups (real and placebo) that could indicate the regression of symptoms by time. In addition, serum levels of inflammatory markers, including IL-10, TNF-α, and CRP decreased significantly, which was greater in the real group. TNF-α, a pleiotropic cytokine, is suggested to play a role in pathogenesis and progression of endometriosis and peritoneal TNF-α values are used for early diagnosis of endometriosis with a high diagnostic accuracy [25]. Li et al. reported significant decreased serum levels of TNF-α after surgery for endometriosis and suggested it for postoperative follow-up [26], which is parallel to the results of the present study. A systemic review determined the effectiveness of anti-TNF treatments (like infliximab) in management of endometriosis [27], which supports our findings. Furthermore, our findings showed decreased level of TNF that confirmed the anti-inflammatory effect of clarithromycin on endometriosis in 6 month follow-up. Therefore, clarithromycin suppressed endometriosis-induced inflammation, but as this review study also indicated, the literature suggests insufficient evidence in this regard [27]. Another cytokine measured in the present study was IL-10, an anti-inflammatory cytokine, inhibiting the production of multiple inflammatory mediators and activating macrophages and dendritic cells, and the results indicated decreased IL-10 by time, although the mean level of IL-10 was higher in the real group than the placebo group, which is consistent with the results of animal models, reporting enhanced expression of IL-10 by clarithromycin that inhibited excess inflammatory reaction and had therapeutic effect on endometriosis lesions, concluding macrolide as a treatment choice for endometriosis [22]. In addition, Suen et al. reported depletion of IL-10 in surgically induced endometriosis of rats that significantly decreased the size of endometrial lesions and in contrast to the results of the

present study, IL-10 administration promoted the growth of endometrial lesions and the authors suggested that IL-10 may suppress the immunity against endometrial implants, contributing to development of endometriosis [28]. In the present study, we hypothesized initially that clarithromycin would increase IL-10 as an anti-inflammatory cytokine, but the results indicated decreased IL-10 in both real and placebo groups, which may be due to the time of sampling, as the decreased inflammation after 3 months could have inhibited the secretion of anti-inflammatory cytokine (IL-10). As the pathophysiology of inflammation in humans may differ from animals, further studies are suggested to elucidate this issue.

Two other markers measured in the present study were ESR and CRP, inflammatory markers with proven role in the pelvic inflammatory process of endometriosis. There is no recommendation in literature for use of ESR in diagnosis of endometriosis, but it can be used as a nonspecific inflammatory marker in diagnosis and follow-up of endometriosis [29]. In our study, ESR significantly changed after 3 and 6 months in both groups, and the increased levels were clinically more significant in the real group, thus the results of the present study cannot recommend ESR as a proper marker for early diagnosis and follow-up. CRP, an acute phase protein, is widely used to monitor ongoing inflammatory and infectious processes and is suggested in endometriosis follow-up [30], but there is no agreement on this issue and some researchers suggest no significant difference between CRP levels between patients with endometriosis and healthy controls [31, 32]. In our study, CRP values significantly decreased after 3 and 6 months in both clarithromycin and placebo groups, but the clarithromycin group showed greater reduction compared to the placebo group. Considering various factors that affect the changes in CRP and ESR must be interpreted with great caution and this study could not suggest CRP and ESR as a marker for follow-up of endometriosis.

This was the first randomized placebo-controlled clinical trial on humans to study the effects of clarithromycin on postsurgical endometriosis. However, there are some limitations with our study. One of the important limitations in this study was relatively short follow-up period and low sample size. In addition, the two groups of real and placebo were not the same size and conducting further statistical analyses such as bootstrapping analyses is required to evaluate the possible overestimation or underestimation of the outcomes.

Conclusion

The findings of this clinical trial showed that clarithromycin can be effective on clinical symptoms of patients with endometriosis and reduce the levels of inflammatory markers, including IL-10, TNF-α, and CRP, in both groups with significantly greater decrease in the real group (receiving clarithromycin) than the placebo group. while there was no significant interaction with the time and the IL-10 and TNF as important markers (these factors decreased in both groups). Therefore, further studies with larger sample size and longer follow-up periods should be conducted to reach a definitive conclusion of the efficacy of clarithromycin.

Author contributions SA: project administration, methodology. TP: conceptualization, validation, writing—review and editing. EA: software, validation, writing—original draft. GD: data curation, formal analysis.

Funding This study was financially supported by Shiraz University of Medical Sciences, Shirza, Iran (Grant No.: 91-01-01-4809).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest on publishing this study.

Ethical approval All of the protocols and experimental procedures of this study were approved by the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Code: IR.sums.rec.1394.S744) which were in complete accordance with the ethical regulations of human studies set by the Helsinki Declaration (2014).

Informed consent Informed consent was obtained from all the patients who participated in this study.

References

1. Eskenazi B, Warner ML (1997) Epidemiology of endometriosis. Obstet Gynecol Clin 24(2):235–258
2. Parazzini F, Vercellini P, Pelucchi C (2012) Endometriosis: epidemiology, and etiological factors. In: Giudice LC, Evers JL, Healy DL (eds) Endometriosis. Blackwell publishing, Hoboken, NJ, pp 19–26. https://doi.org/10.1002/9781444398519.ch2
3. Ozkan S, Murk W, Arici A (2008) Endometriosis and infertility. Ann N Y Acad Sci 1127(1):92–100
4. Harada T (2013) Dysmenorrhea and endometriosis in young women. Yonago Acta Medica 56(4):81
5. Bulletti C et al (2010) Endometriosis and infertility. J Assist Reprod Genet 27(8):441–447
6. Triolo O, Laganà AS, Sturlese E (2013) Chronic pelvic pain in endometriosis: an overview. J Clin Med Res 5(3):153
7. Missmer SA et al (2004) Reproductive history and endometriosis among premenopausal women. Obstet Gynecol 104(5 Part 1):965–974
8. Missmer SA et al (2004) Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 160(8):784–796
9. Fadhlaoui A, Bouquet de la Joliniere J, Feki A (2014) Endometriosis and infertility: how and when to treat? Front Surg 1:1–6. https://doi.org/10.3389/fsurg.2014.00024
10. Caserta D et al (2016) Endometriosis allergic or autoimmune disease: pathogenetic aspects—a case control study. Clin Exp Obstet Gynecol 43(3):354–357

11. Robboy SJ, Bean SM (2010) Pathogenesis of endometriosis. Reprod Biomed Online 21(1):4–5
12. Kim JJ, Kurita T, Bulun SE (2013) Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev 34(1):130–162
13. Barrier BF (2010) Immunology of endometriosis. Clin Obstet Gynecol 53(2):397–402
14. Rafique S, Decherney AH (2017) Medical management of endometriosis. Clin Obstet Gynecol 60(3):485–496
15. Bohler HC et al (2007) Endometriosis markers: immunologic alterations as diagnostic indicators for endometriosis. Reprod Sci 14(6):595–604
16. Wu M-H, Hsiao K-Y, Tsai S-J (2015) Endometriosis and possible inflammation markers. Gynecol Minim Invasive Ther 4(3):61–67
17. Matalliotakis I et al (2012) High rate of allergies among women with endometriosis. J Obstet Gynaecol 32(3):291–293
18. Kanoh S, Rubin BK (2010) Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev 23(3):590–615
19. Luisi F et al (2012) Anti-inflammatory effects of macrolides in childhood lung diseases. Jornal Brasileiro de Pneumologia 38(6):786–796
20. Spyridaki A et al (2012) Effect of clarithromycin in inflammatory markers of patients with ventilator-associated pneumonia and sepsis caused by Gram-negative bacteria: results from a randomized clinical study. Antimicrob Agents Chemother 56(7):3819–3825
21. Zeng M et al (2015) Clarithromycin and dexamethasone show similar anti-inflammatory effects on distinct phenotypic chronic rhinosinusitis: an explant model study. BMC Immunol 16(1):37
22. Umezawa M et al (2011) Clarithromycin and telithromycin increases interleukin-10 expression in the rat endometriosis model. Cytokine 55(3):339–342
23. Cavkaytar S et al (2015) Clarithromycin regresses endometriotic implants in rat endometriosis model. J Obstet Gynaecol 35(8):844–847
24. Sugamata M et al (2004) Effects of clarithromycin on a rat endometriosis model: light and electron microscopic evaluation. Jpn J Antibiot 57:18–20
25. Gupta S et al (2006) Serum and peritoneal abnormalities in endometriosis: potential use as diagnostic markers. Minerva Ginecol 58(6):527
26. Galo S et al (2005) TNF-alpha serum levels in women with endometriosis: prospective clinical study. Ceska Gynekol 70(4):286–290
27. Lu D, Song H, Shi G (2013) Anti-TNF-alpha treatment for pelvic pain associated with endometriosis. Cochrane Database Syst Rev (3):1–29. https://doi.org/10.1002/14651858.CD008088.pub3
28. Suen J-L et al (2014) Serum level of IL-10 is increased in patients with endometriosis, and IL-10 promotes the growth of lesions in a murine model. Am J Pathol 184(2):464–471
29. Jaiyeoba O, Soper DE (2011) A practical approach to the diagnosis of pelvic inflammatory disease. Infect Dis Obstet Gynecol 2011:1–6. https://doi.org/10.1155/2011/753037
30. Riiskjaer M et al (2017) Diagnostic value of serial measurement of C-reactive protein in the detection of a surgical complication after laparoscopic bowel resection for endometriosis. Gynecol Obstet Invest 82(4):410–416
31. Xavier P et al (2006) Serum levels of VEGF and TNF-α and their association with C-reactive protein in patients with endometriosis. Arch Gynecol Obstet 273(4):227–231
32. Kianpour M, Nematbakhsh M, Ahmadi SM (2012) C-reactive protein of serum and peritoneal fluid in endometriosis. Iran J Nurs Midwifery Res 17(2 Suppl 1):S115

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.