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Original Article

Clinical efficacy of levofloxacin hydrochloride plus metronidazole in the treatment of pelvic inflammatory disease: a retrospective analysis

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Abstract: Objective: To investigate the clinical efficacy and safety of levofloxacin (LEV) hydrochloride plus metronidazole (MNZ) in treating pelvic inflammatory disease (PID). Methods: This retrospective study included 80 PID patients and grouped them based on their treatment regimens: a control group (n=40) treated with LEV hydrochloride injection and a research group (n=40) treated with MNZ plus LEV hydrochloride injection. Clinical efficacy, post-treatment inflammatory indexes, hemorheology (high-/low-shear viscosity [HSV/LSV], plasma viscosity [PV]), symptom resolution time, disease recurrence, as well as pre- and post-treatment pelvic mass diameter, pelvic effusion depth, and quality of life, were compared between the two groups. Adverse reactions during treatment and one-year recurrence were also recorded. Results: Compared with the control group, the research group showed a significantly higher total clinical effective rate and faster clinical symptom resolution (including lower abdominal pain, abnormal leucorrhea, lumbosacral pain, urgent micturition, dysuria, and frequent micturition). Besides, the research group showed smaller pelvic mass diameter and pelvic effusion depth, superior quality of life, lower serum inflammatory markers, and reduced HSV, LSV, and PV levels. The one-year recurrence rate was also significantly lower in the research group. Conclusions: LEV hydrochloride combined with MNZ is both effective and safe for the treatment of PID, demonstrating notable advantages in promoting inflammation resolution, improving hemorheological parameters, reducing recurrence, and enhancing quality of life.

Keywords: Levofloxacin, metronidazole, pelvic inflammatory disease, quality of life

Introduction

Pelvic inflammatory disease (PID) is a common gynecological reproductive tract infection caused by the ascent of microorganisms from the vagina or lining of the cervix to the endometrium and fallopian tubes [1]. PID is a general term describing inflammation of the female upper reproductive tract, covering salpingitis, endometritis, oophoritis, tubo-ovarian abscess, and pelvic peritonitis [2]. The disease is mainly seen in young sexually mature women, with the most common onset age being 20-35 years old. An estimated 2.5 million American women aged 18 to 44 have been diagnosed with PID in their lifetime, and 1/8 women with a history of PID experience complications during pregnancy [3]. PID is classified as either acute or chronic, depending on its pathogenesis and clinical manifestations. The symptoms of PID may appear abruptly within a few days or slowly over weeks to months. Long-term PID may lead to tubal infertility, ectopic pregnancy, and chronic pelvic pain [4]. Recent evidence has strongly associated PID with the occurrence of ovarian tumors, and that recurrent episodes of chronic PID not only affect women's reproductive health but also increase family and socioeconomic burdens [5]. The cost of treatment was previously estimated at US$ 1,995 per patient, excluding the cost of future evaluations and treatment of complications [6]. Antibiotics form the cornerstone of PID treatment. Empiric broad-spectrum therapy covering a wide range of pathogens is essential for treatment; however, the optimal regimen has not yet been determined. Currently, single antibiotic use for PID is prone to drug resistance, which reduces treatment efficacy. Therefore, PID is mostly treated with a combination of drugs.

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This study investigated the clinical efficacy of levofloxacin (LEV) hydrochloride combined with antibiotics for PID, hoping to find a more effective medication scheme for the disease and provide a reference for the clinical treatment of PID. Meanwhile, this study offers several innovative aspects. First and foremost, it utilizes retrospective real-world data to provide a comprehensive analysis of the efficacy and safety of the LEV-metronidazole (MNZ) combination regimen in PID-affected individuals. Beyond verifying that the combined treatment brings about a far more notable down-regulation in inflammatory biomarkers [C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6)], this research also illustrated the therapy's value in shrinking pelvic masses, reducing fluid accumulation depth, easing patients' symptoms, and lowering the one-year recurrence likelihood. Another standout feature is the innovative inclusion of quality-of-life assessments as a metric for measuring efficacy. By utilizing multi-dimensional efficacy endpoints, the research successfully validates the benefits of this regimen in actual clinical scenarios. It is necessary to emphasize that this study has several innovative aspects. First, through a rigorous control design, it verified the significant efficacy of LEV plus MNZ compared to LEV alone in PID treatment. Second, from multiple dimensions such as inflammatory indicators, hemorheological indicators, time to symptom resolution, diameter of pelvic masses, depth of pelvic effusion, quality of life, and adverse reactions, the clinical effects of LEV + MNZ in treating PID were systematically evaluated. Finally, through follow-up analysis, it was determined that the combined therapy can prevent 1-year recurrence and can provide patients with better therapy that balances efficacy, safety, and better clinical outcomes.

Patients and methods

Research participants

A retrospective analysis was performed on 80 patients with PID admitted to The First Affiliated Hospital of Xi'an Medical University from July 2020 to July 2022. The patients were divided into a control group (n=40) and a research group (n=40) according to the treatment protocol. This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Medical University.

Inclusion criteria: age between 18 and 50; diagnosis of PID according to the 2017 European Guideline for the Management of PID [7]; confirmed by routine gynecological examinations such as B-ultrasound, color Doppler ultrasound, diagnostic laparoscopy, and vaginal discharge examination; complete clinical data; a history of sexual life; no use of anti-infective drugs in the past 3 months; without surgical indication. Exclusion criteria: concomitant heart, liver, kidney, or other vital organ dysfunction; other infectious diseases; allergies to study medication; irregular vaginal bleeding; communication difficulties; or pregnancy or lactation.

Treatment

Control group: Patients were instructed to rest in bed and follow a high-protein diet. They were advised to avoid spicy food and other irritants such as smoking and alcohol to prevent the aggravation of inflammation. Besides, moderate daily physical activity was encouraged to improve immune and defense capabilities. Patients were given LEV hydrochloride injection (Fuan Pharmaceutical (Group) Ningbo Team Pharm Co., Ltd., State Drug Approval Document Number: H20060509) via intravenous drip at a dose of 0.4 g/time, once a day, for 2 weeks.

Research group: On the basis of the above treatment, MNZ injection (Jiangsu Huayang Pharmaceutical Co., Ltd., State Drug Approval Document Number: H32024431) was further administered intravenously at a dose 0.5 g/time, once a day, for 2 weeks.

Outcome measures

The overall efficacy of the two groups was compared. Marked effectiveness: clinical symptoms were completely resolved after treatment, with imaging revealing basically normal uterine appendages; Effectiveness: clinical symptoms improved after treatment, and imaging indicated persistent uterine hypertrophy compared with normal uterus, with the dark liquid area in the abdominal cavity decreased by more than 65%; Ineffectiveness: no improvement in symptoms nor reduction in uterine hypertrophy or inflammatory masses. Overall clinical effective rate = (marked effectiveness + effectiveness) cases/total cases ×100%.

The time to resolution of various symptoms, including lower abdominal pain, abnormal leu-

corrhea, lumbosacral pain, urinary urgency, dysuria, and frequent urination, were compared between the two groups. Before and after treatment, the pelvic effusion depth and mass diameter were detected by B-ultrasound and MRI, respectively.

The occurrence of adverse reactions during the treatment was recorded, mainly including abnormal liver function, nausea and vomiting, abdominal pain, and dizziness and headache.

Enzyme-linked immunosorbent assays (ELISAs) were performed to determine serum CRP, TNF-α, and IL-6 levels. All the ELISA kits were obtained from Shanghai Cellsolution Biotech Co., Ltd. (EKH159-P, EKH218-P, EKH207-P) and the operation followed the instructions.

Patient hemorheological parameters, such as high-/low-shear viscosity (HSV/LSV) and plasma viscosity (PV), were assessed on a fully automated blood rheology analyzer.

Pre- and post-treatment (4 weeks after treatment) quality of life was assessed using the Short-Form 36 Item Health Survey (SF-36), covering dimensions of general health (GH), role physical (RP), mental health (MH), and bodily pain (BP), each with the highest score of 100. Higher score indicates better quality of life.

Patients were followed up every six months over the one-year follow-up period, and a Doppler ultrasound was performed at each follow-up visit to observe recurrence.

Statistical processing

Sample size estimation was made using PASS 15.0, based on overall efficacy and the formula for comparing two independent proportions. The final calculated effect size (Cohen's h) was 0.52, indicating a moderate effect. With a two-sided significance level of $\alpha=0.05$ and test power (1-β) at 80%, the minimum required sample size for each group was calculated to be 39 cases. The actual sample size of 40 cases per group met the minimum sample size requirement. The specific calculation formula was $n = [Z_{(1-\alpha/2)} * \sqrt{(2 * P * (1-P)) + Z_{(1-\beta)} * \sqrt{(P_1(1-P_1) + P_2(1-P_2))}}]^2/(P_1 - P_2)^2$, where $P = (P_1 + P_2)/2$, and $Z_{(1-\alpha/2)}$ and $Z_{(1-\beta)}$ are the quantiles of the standard normal distribution.

GraphPad Prism 6 was used for data analysis and graphing. Count data were expression as n (%) and compared using the chi-square test. Measurement data were subjected to Bartlett's test for variance homogeneity and Kolmogorov-Smirnov test for normality. Data adhering to a normal distribution are presented in the form of the mean ± standard deviation (SD); independent t-tests were used for comparisons between two groups and paired t-tests for comparisons before and after treatment within the group. For non-normally distributed measurement data, the median (interquartile range) [M(Q1, Q3)] was used for statistical description, and the Mann-Whitney U test was employed to evaluate between-group differences. A *p*-value <0.05 was considered statistically significant.

Results

Comparison of general data between the two groups

No statistical differences were observed between the two groups in terms of age, body mass index (BMI), dietary status, working status, education level, marital status, childbearing history, or disease type (all P>0.05; **Table 1**).

Comparison of clinical efficacy between the two groups

As shown in **Table 2**, the research group demonstrated a significantly higher overall clinical effective rate than the control group (95.00% vs. 77.50; P=0.023).

Comparison of time to clinical symptom resolution between the two groups

As shown in **Table 3**, the research group demonstrated significantly shorter times to clinical symptom resolution, including lower abdominal pain, abnormal leucorrhea, lumbosacral pain, urgent micturition, dysuria, and frequent micturition, compared to the control group (all P<0.05).

Comparison of mass diameter and pelvic effusion depth between the two groups

As shown in **Figure 1**, there were no significant differences in pre-treatment mass diameter or pelvic effusion depth between the two groups (P>0.05). However, both groups showed reductions in the mass diameter and pelvic effusion depth after treatment (P<0.05), with more significant reductions observed in the research group (P<0.05).

Table 1. Comparison of baseline characteristics between the two groups ([n (%)], $\bar{x} \pm sd$)

Groups	Control group (n=40)	Research group (n=40)	$Z/\chi^2/t$	P
Age (years old)	32.00 (25.25, 40.75)	33.00 (27.00, 42.75)	-0.501	0.616
Body mass index (kg/m^2)	23.85±2.11	23.80±2.10	0.106	0.916
Dietary status			0.853	0.356
Regular	17 (42.50)	13 (32.50)		
Irregular	23 (57.50)	27 (67.50)		
Working status			0.621	0.431
Unemployed	32 (80.00)	29 (72.50)		
Employed	8 (20.00)	11 (27.50)		
Educational level			2.257	0.133
≤ high school	26 (65.00)	32 (80.00)		
> high school	14 (35.00)	8 (20.00)		
Marital status			0.952	0.329
Married	26 (65.00)	30 (75.00)		
Single	14 (35.00)	10 (25.00)		
Childbearing history			1.257	0.262
With	19 (47.50)	24 (60.00)		
Without	21 (52.50)	16 (40.00)		
Disease type			0.912	0.340
Acute	15 (37.50)	11 (27.50)		
Chronic	25 (62.50)	29 (72.50)		

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Groups	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=40)	10 (25.00)	21 (52.50)	9 (22.50)	31 (77.50)
Research group (n=40)	22 (55.00)	16 (40.00)	2 (5.00)	38 (95.00)
χ^2	7.500	1.257	5.165	5.165
P	0.006	0.262	0.023	0.023

Table 3. Comparison of clinical symptom resolution time between the two groups (x ± sd, days)

Groups	Lower abdominal pain	Abnormal leucorrhea	Lumbosacral pain	Urgent micturition, dysuria, and frequent micturition
Control group (n=40)	9.60±2.01	9.10±2.37	9.65±2.36	6.33±2.54
Research group (n=40)	6.03±1.94	6.90±2.21	6.43±1.99	4.38±1.55
t	8.083	4.294	6.597	4.145
P	<0.001	<0.001	<0.001	<0.001

Comparison of the incidence of adverse reactions between the two groups

As shown in **Table 4**, the two groups didn't differ significantly in adverse reactions such as abnormal liver function, nausea and vomiting, abdominal pain, or dizziness, yielding comparable overall incidence of adverse reactions (12.50% vs. 22.50%; P>0.05).

Comparison of inflammatory factor levels between the two groups

The two groups exhibited comparable inflammatory factor levels in CRP, IL-6, and TNF-α (P>0.05) before treatment. After treatment, both groups showed notable reductions in these markers (P<0.05), with the research group showing significantly greater reductions

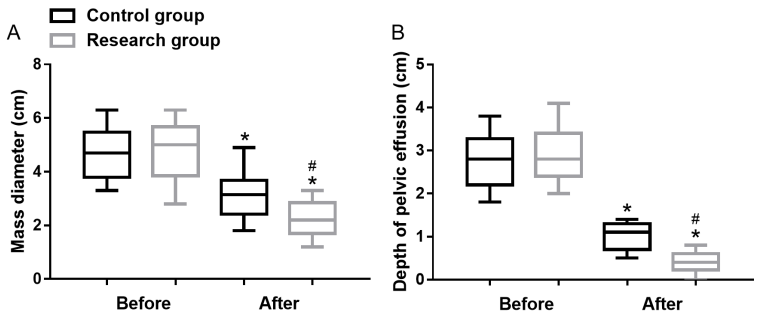

Figure 1. Comparison of mass diameter (A) and pelvic effusion depth (B) between the two groups before and after treatment. Note: *P<0.05 compared with the pre-treatment level in the same group; *P<0.05 compared with the control group during the same period.

compared with the control group (P<0.05, **Figure 2**).

Comparison of hemorheological parameters between the two groups

The hemorheological parameters, including HSV, LSV, and PV were similar between the groups at baseline (P>0.05), but decreased notably in both groups after treatment (P<0.05). Notably, the research group demonstrated significantly greater reductions compared with the control group (P<0.05), as detailed in **Table 5**.

Comparison of quality of life between the two groups

As shown in **Figure 3**, there were no significant differences in quality-of-life scores (determined using SF-36 scale, including the domains of GH, RP, MH, and BP) between the two groups before treatment (P>0.05). After treatment, these scores elevated statistically (P<0.05), with notably higher scores in the research group compared with the control group (P<0.05).

Comparison of the recurrence rate between the two groups

The 6-month and 1-year recurrence rates of the two groups were compared, and the results showed similar recurrence rates between the two groups at the 6-month follow-up (15.00% vs. 5.00%; P>0.05); however, at the one-year follow-up, the recurrence rate was significantly lower in the research group compared with the other group (30.00% vs. 10.00%; P=0.025), as shown in **Table 6**.

Discussion

PID has become a common health issue among women of childbearing age in both developed and developing countries [8]. Research has indicated that approximately 25% of PID patients experience long-term sequelae, including adnexitis, menstrual disorders, infertility, ectopic pregnancy, and chronic pelvic pain [9]. PID is caused by a variety of microorganisms, with *Chlamydia trachomatis*, Neisseria gonorrhoeae, *Mycoplasma genitalium*, as well as some Gram-negative and -positive bacteria being the common pathogens [10]. Antibiotics remain the cornerstone of current treatments, but single antibiotic therapy can easily lead to the development of pathogen resistance, resulting in unsatisfactory long-term efficacy [11]. Some antibiotic regimens recommended in 1970s and 1980s, such as clindamycin, cefoxitin, cefotetan, and fluoroquinolones, are no longer suitable for empiric treatment of PID [12].

LEV is a third-generation quinolone antibacterial drug with potent and broad-spectrum antimicrobial activity, which can inhibit bacterial DNA gyrase and bacterial topoisomerase II, thus blocking DNA replication and exerting antibacterial effects [13]. Meanwhile, LEV is the levorotatory form of ofloxacin, which avoids the side effects produced by the dextrorotatory form of ofloxacin and enhances the antibacterial effect. MNZ is an anti-anaerobic drug belonging to the nitroimidazole class, which can effectively defend a variety of anaerobic bacteria. In an oxygen-free environment, it is reduced to amino derivatives that interfere with the synthesis of bacterial DNA, thus preventing bacterial reproduction and achieving antibacterial effects [14].

The results of this study showed that compared with the control group, the research group had higher overall clinical efficacy, faster clinical symptom resolution, smaller mass diameters, less pelvic effusion depth, a lower one-year recurrence rate, and higher quality of life; moreover, there was no significant inter-group differ-

Table 4. Comparison of incidence of adverse reactions between the two groups [n (%)]

Groups	Abnormal liver function	Nausea and vomiting	Abdominal pain	Dizziness and headache	Total
Control group (n=40)	0 (0.00)	2 (5.00)	1 (2.50)	2 (5.00)	5 (12.50)
Research group (n=40)	1 (2.50)	2 (5.00)	3 (7.50)	3 (7.50)	9 (22.50)
χ^2	1.013	0	1.053	0.213	1.385
P	0.314	>0.999	0.305	0.644	0.239

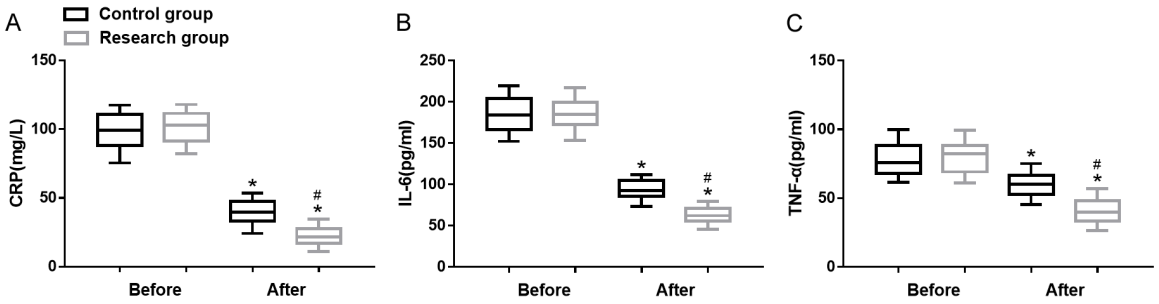

Figure 2. Comparison of serum inflammatory factors between the two groups before and after treatment. A: C-reactive protein (CRP); B: Iinterleukin-6 (IL-6); C: Tumor necrosis factor-α (TNF-α). Note: *P<0.05 compared with the pre-treatment level in the same group; *P<0.05 compared with the control group during the same period.

Table 5. Comparison of hemorheological parameters between the two groups [n (%)]

Groups	Control group (n=40)	Research group (n=40)	t	P
HSV (mPa·s)				
Before treatment	13.25±4.14	14.03±3.63	0.896	0.373
After treatment	5.97±1.19*	5.33±1.25**	2.345	0.022
LSV (mPa·s)				
Before treatment	15.35±3.72	16.32±3.03	1.279	0.205
After treatment	9.70±1.87*	7.65±1.48**	5.437	<0.001
PV (mPa·s)				
Before treatment	6.97±2.02	7.35±1.83	0.882	0.381
After treatment	5.12±1.86*	3.55±1.11**	4.584	<0.001

Note: HSV/LSV, high-/low-shear viscosity; PV, plasma viscosity; *P<0.05, **P<0.01 compared with baseline within each group.

ence in the incidence of adverse reactions. Although the overall incidence of adverse reactions (abnormal liver function, nausea and vomiting, abdominal pain, and dizziness and headache) was higher numerically in the research group, most of the reported events were mild to moderate in severity and did not result in treatment disruption or special medical intervention. This suggests that the LEV + MNZ is both effective and safe for PID management, with treatment-emergent adverse events not significantly compromising treatment adherence and overall patient benefit. The reason is that MNZ and LEV exert antibacterial effects through different mechanisms, enabling them to simultaneously exert their respective antibacterial effects. Although LEV has broad-spectrum antibacterial activities, its effect on anaerobic bacteria is poor, while MNZ happens to be effective against a variety of anaerobic bacteria. The combination of the two broadens pathogen coverage, thereby increasing the efficacy of treatment. On the other hand, both LEV and MNZ are primarily metabolized by the liver. Their combination may, to some extent, increase the metabolic burden on the liver. Meanwhile, both agents can cause gastrointestinal discomfort (e.g., nausea, vomiting, abdominal pain) and

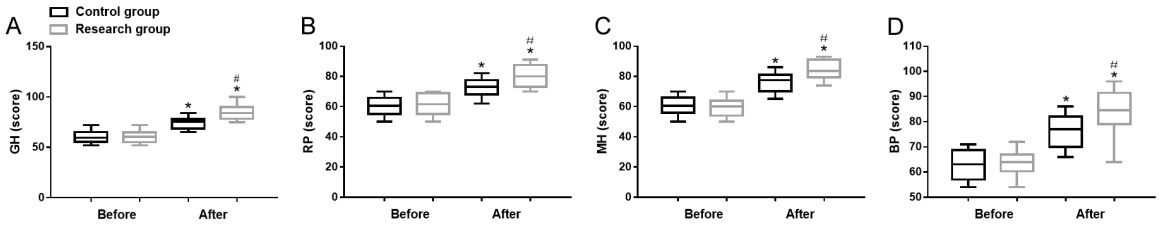

Figure 3. Comparison of quality-of-life scores between the two groups before and after treatment. A: General health (GH) scores; B: Role-physical (RP) scores; C: Mental health (MH) scores; D: Bodily pain (BP) scores. Note: *P<0.05 compared with the pre-treatment level in the same group; *P<0.05 compared with the control group during the same period.

Table 6. Comparison of recurrence rate between the two groups [n (%)]

Groups	At 6-month follow-up	At one-year follow-up
Control group (n=40)	6 (15.00)	12 (30.00)
Research group (n=40)	2 (5.00)	4 (10.00)
χ^2	2.222	5.00
P	0.136	0.025

central nervous system reactions (dizziness, headache, etc.), thereby exerting cumulative toxic effects on the patient's gastrointestinal and nervous systems. Therefore, the combined medication showed a higher overall incidence of adverse reactions numerically [15-18]. The enhanced quality of life in patients in the research group can be attributed to optimized therapeutic effect and improved clinical symptom alleviation on the premise of not increasing adverse reactions, thereby maximizing patients' quality of life. Mikamo H et al. [19] reported that MNZ showed excellent efficacy and good tolerance in patients with infectious peritonitis, abdominal abscesses, and PID, similar to our results.

PID is an inflammatory disease caused by acute inflammatory processes in the pelvic cavity and surrounding tissues [20]. When pathogens invade the pelvic organs, the host immune system activates defensive responses aimed at eliminating these foreign invaders. During this process, the immune system releases a variety of cytokines and chemokines that recruit immune cells to the infection site and trigger inflammatory reactions [21]. CRP, IL-1β, and IL-6 are three key proinflammatory cytokines, with elevated levels in the upper reproductive tract during pathogen infection [22, 23]. At the inflammatory site, these proinflammatory cytokines stimulate the proliferation and activation of leukocytes and enhance the production of chemokines, leading to the recruitment of hematopoietic immune cells and stimulating the proliferation and activation of leukocytes, further exacerbating the inflammatory reaction [24] and increasing the risk of tissue damage and structural diseases in the upper reproductive tract. Therefore, reducing pro-inflammatory mediators is a therapeutic strategy for PID. The results of this study showed that CRP, IL-6, and TNF-α levels were markedly reduced in both groups after treatment, with even lower levels in the research group, suggesting that LEV + MNZ is effective in alleviating inflammation in PID. Previous study indicates that MNZ intervention for acute PID effectively reduces the risk of infections caused by *Atopobium*, anaerobic Gram-negative bacilli, or anaerobic Gram-positive cocci, and decreases the possibility of *Gardnerella* and aspergillosis development in the endometrium [1]. Further evidence suggests that LEV + MNZ for simple PID can eradicate multiple pathogens (e.g., *Escherichia coli*, anaerobic bacteria, *Chlamydia trachomatis*, *Mycobacterium hominis*, *Ureaplasma urealyticum*) [25]. These findings partially explain the anti-inflammatory benefits of the combined regimen in this study, attributing it to the synergistic antibacterial effect. Hemorheology can also serve as an indirect indicator of inflammatory response in PID [26]. In this study, LEV + MNZ exerted notable effects on hemorheology, suggesting that the therapy mitigates inflammatory responses at both systemic and local levels, ultimately improving pelvic microcirculation and promoting inflammation clearance. The treatment of chronic PID with MNZ +

ceftriaxone sodium + Fukejing capsules has been shown to significantly reduce hemorheological indicators (HSV/LSV, PV), thereby effectively lowering blood viscosity [27], consistent with our observations.

This study still has several shortcomings. First, the optimal dosage of LEV plus MNZ in the treatment of PID has not been investigated. Second, the follow-up duration of this study was only one year, making it impossible to evaluate the long-term reproductive-related outcomes, such as recurrence, infertility, and ectopic pregnancy. Third, the subjects of this study are young and middle-aged women, so our results may not be applicable to other patient populations. Finally, the small sample size of only 80 cases may affect the accuracy of the research results. Future studies should conduct large-scale research to further verify these findings.

Conclusion

The combined use of MNZ and LEV for PID management enhances therapeutic outcomes by mitigating inflammation, normalizing hemorheological parameters, and accelerating symptom resolution. Moreover, it is associated with a reduced recurrence risk and an enhanced quality of life, while exhibiting a high safety profile, supporting its potential for broader clinical application.

Disclosure of conflict of interest

None.

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