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Efficacy and safety of levornidazole disodium phosphate for the treatment of pelvic inflammatory disease: A multicenter, double-blind, randomized trial

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ABSTRACT

Objective: To compare the efficacy and safety of levornidazole and levornidazole disodium phosphate in women with pelvic inflammatory disease.

Methods: Women from 12 hospitals in China received a 14-day treatment course comprising 7 days of intravenous therapy followed by 7 days of oral sequential therapy: intravenous levornidazole 0.5 g twice daily (Group A, n=49), levornidazole disodium phosphate 1.0 g once daily (Group B, n=49), or levornidazole disodium phosphate 0.5 g twice daily (Group C, n=46), followed by oral levofloxacin plus ornidazole for 7 days.

Results: Of the 144 patients in the full analysis set (FAS), 131 (91.00%) were included in the per-protocol set and 38 (29.00%) were microbiologically valid. In the FAS, clinical cure rates at day 14 were 77.55%, 83.67%, and 82.61% for Groups A, B, and C, respectively (P=0.745). Bacteriological clearance rates were 76.47%, 93.75%, and 100.00%, respectively (P=0.248). Drug-related adverse events occurred less frequently in Group B than in Group A (38.78% *vs*. 61.22%; P=0.025).

Conclusions: Daily administration of levornidazole disodium phosphate achieved clinical and bacteriological efficacy comparable to twice-daily levornidazole in women with pelvic inflammatory disease and was associated with significantly fewer drug-related adverse events.

KEYWORDS: Pelvic inflammatory disease; Levornidazole disodium phosphate; Multicenter; Randomized controlled; Double-blind

Summary

Question: What is the comparative efficacy and safety of levornidazole versus levornidazole disodium phosphate in women with pelvic inflammatory disease?

Findings: In this multicenter, double-blind, randomized trial, clinical and bacteriological cure rates were similar across all three treatment groups with no significant differences. Once-daily levornidazole disodium phosphate caused significantly fewer drug-related adverse events than twice-daily levornidazole.

Meaning: Once-daily levornidazole disodium phosphate is similarly effective but better tolerated for treating pelvic inflammatory disease in women.

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1. Introduction

Pelvic inflammatory disease (PID) involves a spectrum of upper genital tract infections and inflammations, including endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess, and pelvic peritonitis[1,2]. It primarily affects sexually active women of reproductive age and is commonly associated with sexually transmitted pathogens such as *Neisseria gonorrhoeae* and *Chlamydia* (*C.*) *trachomatis*, as well as endogenous anaerobic bacteria, *Mycoplasma genitalium* and *Ureaplasma urealyticum* in some cases[3–5,6,7]. Untreated or inadequately treated PID may result in serious reproductive sequelae, including infertility, ectopic pregnancy, and chronic pelvic pain, making PID an important public health concern[8,9]. However, because the clinical manifestations of PID are often nonspecific and the diagnostic accuracy of clinical criteria remains limited, its true incidence is difficult to determine[10].

Common clinical manifestations include lower abdominal pain, deep dyspareunia, abnormal uterine bleeding, and abnormal vaginal or cervical discharge; whereas physical findings may include lower abdominal tenderness, adnexal tenderness, cervical motion tenderness, and fever (>38 ℃).

The goals of antimicrobial therapy for PID are to eradicate infection, control symptoms, and prevent long-term sequelae[11]. Owing to polymicrobial nature of PID, broad-spectrum and combination antibiotic regimens are recommended in current United States and Europe guidelines[12,13]. Metronidazole, a nitroimidazole antimicrobial, is commonly included to improve anaerobic coverage[14,15]. However, prolonged worldwide use of metronidazole has been associated with adverse effects, including metallic taste, nausea, transient neutropenia, and peripheral neuropathy, as well as increasing antimicrobial resistance[16–18]. One study demonstrated that the resistance rate of *Bacteroides fragilis* to metronidazole was 38.46%[19]. Therefore, alternative nitroimidazole agents with improved efficacy and tolerability are needed.

Levornidazole is a third-generation nitroimidazole antimicrobial that is used worldwide as an alternative to metronidazole. Levornidazole is used to treat protozoan and bacterial infections. Its mechanism of action involves reactivation by reduction of the nitro group and production of toxic derivatives and radicals[20]. The recommended dose of levornidazole is 0.5 g twice-daily given intravenously.

Levornidazole disodium phosphate, a national class Ⅰ antimicrobial entity as classified by the Chinese National Medical Products Administration (NMPA), demonstrates greater activity and lower toxicity than metronidazole[21,22]. The chemical modification from levornidazole to levornidazole disodium phosphate enhances water solubility and stability, thereby improving its pharmacokinetic profile and supporting a once-daily administration regimen[23,24]. In cases of PID or appendicitis, 1.0 g of this antimicrobial is administered intravenously once daily. However, clinical evidence for the once-daily regimen of levornidazole disodium phosphate in PID remains insufficient. Therefore, this study aimed to test whether the efficacy and safety of once-daily intravenous levornidazole disodium phosphate are non-inferior to the conventional twice-daily intravenous levornidazole regimen in women with PID.

2. Methods

2.1. Study setting

This multicenter, double-blind, randomized, parallel-group study was conducted between May 2018 and January 2019 in China in strict accordance with the Declaration of Helsinki, and all clinical work was subject to the Good Clinical Practice Guidelines. Before any study procedures were performed, full written informed consent was obtained from all participants. All patients were evaluated at the following visits: pretreatment visit (24 hours before the treatment initiation), in-therapy visit (days 2-10), first visit after treatment (Day 7, immediately after completion of intravenous therapy), and a test-of-cure (TOC) visit (Day 14, after completion of the full 14-day treatment course). The primary outcome (clinical efficacy) was assessed at the TOC visit on Day 14.

2.2. Diagnostic criteria

The diagnosis of PID was based on the presence of all following signs and symptoms: pelvic discomfort, lower abdominal tenderness, and cervical motion tenderness as well as at least one of the following signs: pyrexia (axillary temperature >37.8 ℃), a white blood cell (WBC) count >10×10^9/L on routine blood examination, mucopurulent cervical discharge, elevated vaginal discharge WBC as determined *via* microscopy (>15/HP), and elevated C-reactive protein.

2.3. Inclusion and exclusion criteria

The study included women with PID aged 18-65 years. The exclusion criteria for this study were allergy to nitroimidazole, impaired liver or renal function, recent delivery or abortion, severe systemic diseases likely to affect therapy (*e.g.*, cardiovascular abnormalities, unstable angina, high blood pressure, severe neuropathy, or epilepsy), and a history of surgery in the previous 1 month.

2.4. Randomization, blinding, and interventions

Before treatment, participants were assigned to one of three groups: two groups receiving levornidazole disodium phosphate and one group receiving levornidazole. Group assignment was conducted using computer-generated random numbers. The randomization list and drug numbers were generated using the proc plan procedure of SAS 9.4 version. A random list of patients was created using the block randomization method with a 1:1:1 allocation ratio for the three groups, using a fixed block size of 4. To ensure allocation concealment, the group assignment information was sealed in sequentially numbered, opaque, sealed envelopes. Each envelope was opened by the treatment administrator, and outcome assessors remained blinded to group assignments throughout the study period.

Because the three treatment regimens involved different dosing frequencies (levornidazole 0.5 g twice daily in Group A, levornidazole disodium phosphate 1.0 g once daily in Group B, and levornidazole disodium phosphate 0.5 g twice daily in Group C), a double-dummy design was implemented to maintain double blinding. Specifically, participants in the once-daily group (Group B) received active drug once daily plus a matching placebo at the second dosing time each day. Participants in the twice-daily groups (Groups A and C) received active drug twice daily. All placebo preparations were identical in appearance, packaging, labeling, and administration schedule to the corresponding active medications. This double-dummy strategy ensured that all participants received the same number of intravenous infusions per day, thereby preserving blinding for participants, investigators, study coordinators, outcome assessors, and statisticians.

Emergency unblinding procedures were predefined in the study protocol. Unblinding could only be performed in cases of medical necessity (*e.g.*, serious adverse events requiring knowledge of the assigned treatment for clinical management). The randomization code was securely maintained by an independent data management team and was not accessed until after database lock. No emergency unblinding occurred during the conduct of this study.

Group A (control) received 0.5 g of levornidazole intravenously twice a day for 7 days, followed by 7 days of oral therapy (total treatment duration: 14 days). Group B received 1.0 g of levornidazole disodium phosphate intravenously once a day for 7 days, followed by 7 days of oral therapy (total treatment duration: 14 days). Group C received 0.5 g of levornidazole disodium phosphate intravenously twice a day for 7 days, followed by 7 days of oral therapy (total treatment duration: 14 days). All patients were switched to oral medication after 7 days of intravenous infusion, which included one capsule of levofloxacin hydrochloride (0.1 g) twice a day, followed by two capsules of ornidazole (500 mg) twice a day for 7 consecutive days, resulting in a treatment duration of 14 days. This oral regimen was pre-specified and standardized for all patients, based on Chinese guidelines for the management of pelvic inflammatory disease, ensuring consistent follow-up therapy across treatment groups[25]. Levornidazole disodium phosphate was purchased from Yangzijiang Pharmaceutical Co., Ltd., China (approval batch No. 17072011 by CFDA). Levornidazole was purchased from Sanhome Pharmaceutical Co., Ltd. (Nanjing, China; approval batch No. 17121241 by CFDA). Microbiological assessments were performed on endocervical specimens at all three instances, including before treatment, at the first visit after treatment, and at the TOC visit. Safety evaluations, including patient compliance assessments, physical examinations, and clinical laboratory assessments, were also performed before treatment, at the first visit after treatment, and at the TOC visit.

2.5. Primary outcome

The primary outcome of this study included the clinical efficacy after 14 days of treatment, which was determined based on improvement in the clinical signs and symptoms in patients with PID. Based on the evaluation criteria, the curative effect was recorded as cure or failure as follows: (1) the effect was considered as cure when the patient's signs and symptoms at follow-up were resolved, when the condition disappeared or all functions returned to normal, and nonmicrobiological indicators such as imaging and laboratory examination were normal. (2) The effect was considered as failure when, at the end of treatment and follow-up, all signs and symptoms were the same as those at the time of enrollment or did not completely disappear or worsen, when there were new signs or symptoms of the disease, and/or when other antibacterial treatment measures for the disease had to be continued.

2.6. Secondary outcomes

Bacteriological efficacy after 7 and 14 days of treatment was determined based on the microbiological clearance, which was recorded as Clear, Assumed Clear, Unclear, Assumed Unclear; or Other, which referred to other common outcomes by microbial outcome, such as flora alternation, double infection, recurrence, and colonization.

Comprehensive efficacy evaluation refers to the comprehensive analysis and judgment of the signs and symptoms and the results of imaging, laboratory examination, and pathogenic examination of patients with positive bacterial culture before and after treatment. Efficacy was evaluated after comprehensive consideration of the clinical and bacteriological results and was categorized into recovery and invalidity. Recovery refers to patients who are

clinically cured at the post-treatment visit and exhibit bacterial clearance or presumed clearance; invalidity refers to patients who are clinically inactive or exhibit no bacterial clearance, presumed nonclearance or partial clearance, or both at the end of treatment visit. If one of the patient's clinical and bacteriological outcomes was invalidity and the other was missing, the combined treatment effect was considered invalidity.

2.7. Safety evaluations

Data from all patients who received at least one dose of the study drug were used to assess the causality and severity of adverse events, including standard laboratory tests, vital signs examination, and adverse events.

2.8. Statistical analysis

Intention-to-treat (ITT) principle was applied. The Full Analysis Set (FAS), referred to as the ITT set, included all randomized participants who received at least one dose of the study drug and had at least one post-randomization efficacy observation. The Per-Protocol Set (PPS) was a subset of the FAS and comprised participants who completed the full treatment course without major protocol deviations (*e.g.*, good compliance, no prohibited concomitant medications). The microbiological FAS (mFAS) was defined as participants in the FAS with positive baseline bacterial cultures. The microbiological PPS (mPPS) was defined as participants in the PPS with a positive baseline bacterial culture. The hierarchical relationships among the analysis sets are as follows: FAS (ITT) ⊇ PPS, FAS ⊇ mFAS, PPS ⊇ mPPS, and mFAS ⊇ mPPS. Primary efficacy analyses were performed on both the FAS and PPS to assess robustness of the results. Secondary efficacy outcomes (bacteriological efficacy and comprehensive efficacy) were evaluated using the mFAS and mPPS. Safety analyses were conducted on all participants who received at least one dose of the study drug.

Although the study was originally designed as a superiority/comparative trial (two-sided testing with α=0.05), we conducted post-hoc exploratory non-inferiority analyses to address the reviewer's request and to provide additional context for interpreting the observed treatment effects. A non-inferiority margin (δ) of -15% for the difference in clinical cure rates (test minus control) was adopted based on (1) historical antibiotic trials in pelvic inflammatory disease where placebo-adjusted treatment effects typically ranged from 10% to 20%, and (2) clinical judgment that a loss of up to 15% in absolute cure rate would be acceptable given the potential

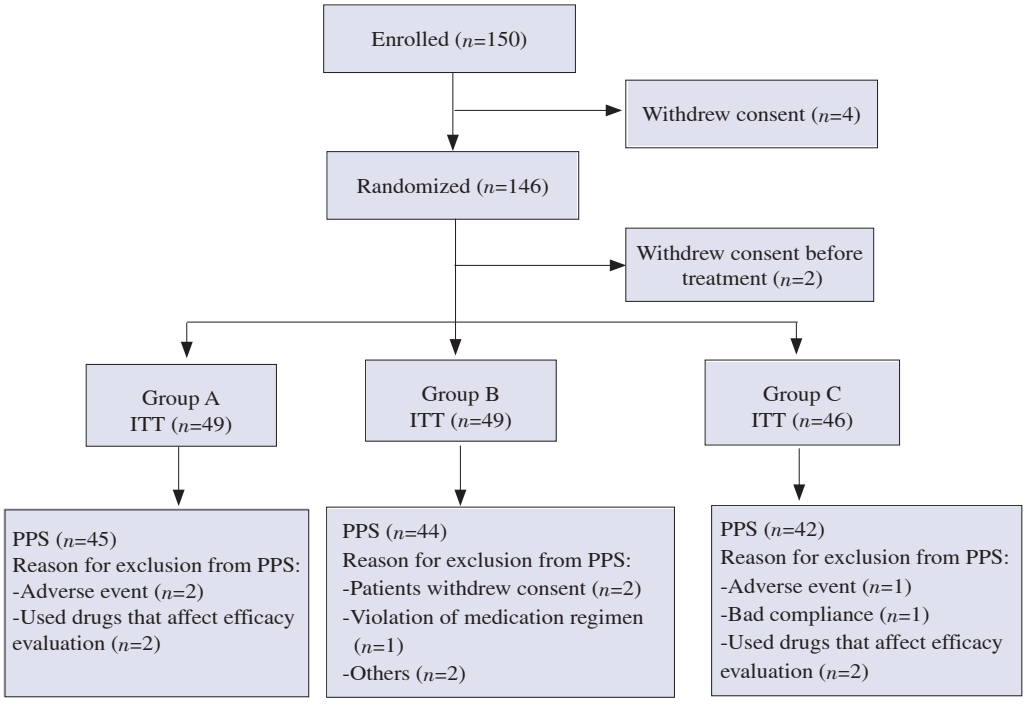

Figure 1. Flowchart of the clinical trial of levornidazole disodium phosphate for pelvic inflammatory disease. Group A received 0.5 g of levornidazole intravenous infusion twice a day for 7 days, followed by oral medication for 7 days; Group B received 1.0 g of levornidazole disodium phosphate intravenous infusion once a day for 7 days, followed by oral medication for 7 days; Group C received 0.5 g of levornidazole disodium phosphate intravenous infusion twice a day for 7 days, followed by oral medication for 7 days. ITT: Intention-to-treat; PPS: Per-Protocol Set.

advantages of a once-daily regimen and the improved safety profile of levornidazole disodium phosphate. Non-inferiority was assessed using one-sided 97.5% confidence intervals (equivalent to two-sided 95% *CI*s for the difference). The test regimen was considered non-inferior to the control if the lower bound of the one-sided 97.5% *CI* for the difference (test-control) exceeded -15%. The same margin (-15%) was applied to secondary efficacy endpoints (bacteriological clearance and comprehensive recovery rate). Importantly, due to the *post-hoc* and exploratory nature of these analyses and the limited sample size (approximately 49 patients per group, which is substantially smaller than the approximately 112 patients per group required for a definitive non-inferiority trial with 80% power at a one-sided α=0.025), the non-inferiority results should be interpreted as hypothesis-generating rather than confirmatory. All *post-hoc* non-inferiority analyses were performed using SAS 9.4. Two-sided testing was performed for all analyzes, with a significance level of 0.05; a 95% confidence interval was calculated for the difference.

2.9. Study protocol

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Approval No. 2017-MD-294) prior to patient enrollment, and the study was conducted in strict accordance with the regulatory and ethical standards in effect at that time. Although prospective registration is currently recognized as an international best practice, it was not a mandatory requirement for phase Ⅱ exploratory clinical trials in China when this study was initiated in 2018. Following the subsequent update of Chinese clinical trial registration policies and in alignment with the International Committee of Medical Journal Editors (ICMJE) recommendations on research transparency, the investigators registered the trial retrospectively (ChiCTR2300073123) to ensure full public disclosure. We confirm that all outcomes reported in this manuscript are consistent with the registered protocol, and no data were selectively reported or altered after registration.

3. Results

3.1. Patient recruitment

A total of 150 women with PID were screened for eligibility. Of these, 146 were randomized to the three treatment groups. However, two participants (one in Group B and one in Group C) withdrew consent before receiving the first dose of the study drug and were therefore not treated. Consequently, 144 patients (49 in Group A, 49 in Group B, and 46 in Group C) received at least one dose of the study medication and were included in the Full Analysis Set (FAS) and Safety Set (SS) (Figure 1).

3.2. Participant characteristics

There were no significant differences between the treatment groups in terms of demographic characteristics, such as age, ethnicity, height, weight, and body mass index (Table 1). In terms

Table 1. Baseline demographics and disease characteristics of patients.

Item	Group A (n=49)	Group B (n=49)	Group C (n=46)	Total (n=144)	F value	P-value
Age, mean±SD, years	38.41±10.41	36.31±7.02	36.65±8.81	37.13±8.84	0.79#	0.457
Ethnicity, n (%)						>0.999
Han	47 (95.92)	46 (93.88)	44 (95.65)	137 (95.14)	-	
Others	2 (4.08)	3 (6.12)	2 (4.35)	7 (4.86)	-	
Height, mean±SD, cm	160.20±5.07	159.08±4.21	160.26±4.60	159.84±4.64	0.99#	0.373
Weight, mean±SD, kg	57.23±7.71	57.40±7.93	57.48±8.15	57.37±7.87	0.01#	0.988
BMI, mean±SD, kg/m^2	22.28±2.72	22.69±3.07	22.35±2.90	22.44±2.89	0.28#	0.754
Temperature, mean±SD, ℃	36.58±0.30	36.59±0.34	36.75±0.46	36.64±0.38	3.13#	0.047
Heart rate, mean±SD, bpm	77.44±8.88	77.61±10.00	78.63±9.50	77.89±9.41	0.22#	0.806
Breathing, mean±SD, bpm	18.85±1.43	18.70±1.61	18.74±1.47	18.77±1.50	0.13#	0.877
Systolic pressure, mean±SD, mmHg	111.96±10.81	110.98±13.67	114.88±11.84	112.57±12.18	1.22#	0.298
Diastolic pressure, mean±SD, mmHg	70.67±8.94	71.29±10.15	72.67±8.15	71.52±9.10	0.56#	0.575
Previous surgery, n (%)	22 (44.90)	26 (53.06)	22 (47.83)	70 (48.60)	-	0.728
Previous infection, n (%)	8 (16.33)	4 (8.16)	5 (10.87)	17 (11.81)	-	0.471
Previous ectopic pregnancy, n (%)	1 (2.04)	0 (0.00)	0 (0.00)	1 (0.69)	-	>0.999
Vaginal infection, n (%)	7 (14.29)	8 (16.33)	8 (17.39)	23 (15.97)	-	0.959
Bacterial vulvovaginitis, n (%)	1 (2.04)	0 (0.00)	1 (2.17)	2 (1.39)	-	0.767
Oophoritic cyst, n (%)	1 (2.04)	1 (2.04)	0 (0.00)	2 (1.39)	-	>0.999

Group A: 0.5 g of levornidazole intravenous infusion twice a day for 7 days, followed by oral medication for 7 days; Group B: 1.0 g of levornidazole disodium phosphate intravenous infusion once a day for 7 days, followed by oral medication for 7 days; Group C: 0.5 g of levornidazole disodium phosphate intravenous infusion twice a day for 7 days, followed by oral medication for 7 days. -: not applicable. #One-way ANOVA was used, otherwise, *Chi*-square test.

Table 2. Fourteen-day clinical efficacy of full analysis set (FAS) and per-protocol set (PPS).

Population	Parameter	Group A	Group B	Group C	*P*-value
FAS	Cure, *n*/*N* (%)	38/49 (77.55)	41/49 (83.67)	38/46 (82.61)	0.745
	95% *CI*	(63.38, 88.23)	(70.34, 92.68)	(68.58, 92.18)	
PPS	Cure, *n*/*N* (%)	36/45 (80.00)	40/44 (90.91)	36/42 (85.71)	0.333
	95% *CI*	(65.40, 90.42)	(78.33, 97.47)	(71.46, 94.57)	
Pairwise comparisons (FAS)	Rate difference, % (95% *CI*)	A-B: -6.12 (-26.44, 14.58)	B-C: 1.06 (-19.13, 21.27)	A-C: -5.06 (-24.92, 15.38)	
Pairwise comparisons (PPS)	Rate difference, % (95% *CI*)	A-B: -10.91 (-31.27, 9.52)	B-C: 5.19 (-15.57, 26.47)	A-C: -5.71 (-26.68, 15.66)	

FAS: Full Analysis Set; PPS: Per-Protocol Set. Pearson χ^2 was used.

Table 3. Fourteen-day bacteriological efficacy (mFAS).

Bacteriological efficacy	Group A (*n*=17)	Group B (*n*=16)	Group C (*n*=9)	*P*-value
Clear, *n* (%)	13 (76.47)	15 (93.75)	9 (100.00)	0.248
95% *CI*	(50.10, 93.19)	(69.77, 99.84)	(66.37, 100.00)	
Assumed clear	0 (0.00)	0 (0.00)	0 (0.00)	
Unclear	2 (11.76)	0 (0.00)	0 (0.00)	
Assumed unclear	0 (0.00)	0 (0.00)	0 (0.00)	
Other	2 (11.76)	0 (0.00)	0 (0.00)	
Missing	0 (0.00)	1 (6.25)	0 (0.00)	
Rate difference, % (95% *CI*)	A-B: -17.28 (-49.16, 15.85)	B-C: -6.25 (-44.47, 32.86)	A-C: -23.53 (-60.01, 17.86)	

Note: Microbiological FAS (mFAS) was defined as those participants in the full analysis set with positive bacterial cultures at baseline. Fisher's exact test was used.

Table 4. Comparison of changes in total clinical signs and symptom total scores before and after treatment (mFAS)

Time		Group A	Group B	Group C	*F* value	*P*-value
3 days after treatment	Mean±SD[#]	-3.02±1.72	-2.43±1.45	-2.41±2.02	1.72[^]	0.184
	t	11.67	10.85	7.44		
	P-value	<0.001	<0.001	<0.001		
7 days after treatment	Mean±SD[#]	-4.26±1.85	-3.70±1.96	-4.35±2.08	1.39[^]	0.253
	t	15.79	12.54	13.71		
	P-value	<0.001	<0.001	<0.001		
14 days after treatment	Mean±SD[#]	-4.72±1.56	-4.26±1.93	-4.77±1.95	1.13[^]	0.327
	t	20.81	15.13	16.03		
	P-value	<0.001	<0.001	<0.001		

[#] Paired *t*-test was used. The *t* and corresponding *P*-value in each cell represent paired *t*-test results for intra-group comparison of symptom total scores between post-treatment timepoint within Group A, Group B and Group C, respectively. [^]One-way ANOVA was used.

of patients with a history of surgery, two (4.08%) each in Groups A and B had undergone salpingectomy. Eight (16.33%) patients in Group A had a history of previous infection, including two patients with vaginal infection, one with pelvic inflammation, and one with vulvovaginal candidiasis. In addition, one patient in Group A had a previous ectopic pregnancy. With regard to current symptoms, similar numbers of patients in Groups A, B, and C had vaginal infections (14.29%, 16.33%, and 17.39%), bacterial vulvovaginitis (2.04%, 0.00%, and 2.17%), and oophoritic cysts (2.04%, 2.04%, and 0.00%), respectively. Medical history and current medical conditions might be related to the occurrence of PID.

3.3. Microbiology

Overall, 29.17% (42/144) of all patients tested positive for bacteria. *Prevotella bivia* (13 strains, 25.49%) was the most common pathogen, followed by *Veillonella* (six strains, 11.76%), anaerobic *Streptococcus* (five strains, 9.80%), and *Finegoldiamagna* (four strains, 7.84%; Supplementary Table 1).

3.4. Clinical efficacy

Among those receiving levornidazole disodium phosphate (Groups B and C), 41 and 38 patients were cured after treatment, with a cure rate of 83.67% and 82.61%, respectively. In the control Group A, 38 patients were cured, with a cure rate of 77.55%. Further, as per the clinical efficacy criteria, levornidazole disodium phosphate therapy was clinically comparable with levornidazole therapy (Table 2). The clinical data of PPS population were consistent with those of ITT population (Table 2). There was no significant difference between the groups in terms of blood, urine, liver, and kidney functions ($P>0.05$).

3.5. Bacteriological efficacy

A total of 25 bacterial strains were culture-positive in Groups B

Table 5. Comparison of adverse events and adverse reactions.

	Group A (n=49)		Group B (n=49)		Group C (n=46)		P-value
	No. of events	Cases (%)	No. of events	Cases (%)	No. of events	Cases (%)	
AE	67	30 (61.22)	42	19 (38.78)	65	23 (50.00)	0.093
AR	35	19 (38.78)	15	9 (18.37)	21	10 (21.74)	0.059
SAE	0	0 (0.00)	0	0 (0.00)	2	2 (4.35)	0.101
SAR	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	-

AE, adverse events; AR, adverse reactions; SAE, serious adverse events; SAR, serious adverse reactions. Adverse reactions refer to adverse events with a test drug relationship of "definitely related," "very likely related," or "possibly related."

and C before treatment, of which 15 strains (93.75%) in Group B and 9 (100.00%) in Group C were eliminated after treatment. In total, 17 bacterial strains in the control Group A were detected before treatment, among which 13 strains were eliminated (clearance rate, 76.47%) after treatment, whereas 2 strains were detected. The clearance rates were 76.47% (13/17) in Group A, 93.75% (15/16) in Group B, and 100.00% (9/9) in Group C, with no statistically significant difference among the three groups (P=0.248; Table 3). The bacteriological efficacy of each group after 7 days of treatment was similar to that after 14 days of treatment, with a clearance rates of 82.35%, 81.25%, and 77.78% for Groups A, B, and C, respectively. The bacteriological efficacy of PPS was consistent with that of the ITT population.

3.6. Comprehensive efficacy

According to the comprehensive efficacy evaluation mentioned above, 14 and 8 patients were categorized under recovery after 14 days of treatment in the Groups B and C with recovery rates of 87.50% and 88.89%, respectively. In the control Group A, 11 cases were categorized under recovery, with a recovery rate of 64.71%. Based on the criteria for comprehensive efficacy, levornidazole disodium phosphate therapy was clinically comparable to levornidazole therapy (Supplementary Table 2). Moreover, the comprehensive efficacy data after the 7-day treatment was consistent with those after 14-day treatment. Similar results were observed on comparing the total scores of the clinical signs and symptoms of each group with the baseline change value after treatment. After 3, 7, and 14 days of treatment, the total score of clinical signs and symptoms in each group decreased compared with baseline (Table 4).

3.7. Safety

In terms of safety, in the ITT population, the incidence of adverse events was 61.22% (30/49, 61.22%) in Group A, 38.78% (19/49) in Group B, and 50.00% (23/46) in Group C. Compared with Group A, Group B showed a significantly lower incidence of adverse events (Pearson χ^2=4.939, P=0.026) and adverse reactions (38.78% *vs*. 18.37%, Pearson χ^2=5.000, P=0.025). No other between-group differences reached statistical significance (Table 5). Detailed adverse events with an incidence of $\geqslant$5% in groups are summarized in Supplementary Table 3.

All adverse events were mild in severity, except for two cases in Group C: one with endometrorrhagia and one with hypertension. The most common adverse reactions occurred in the control Group A, including skin or subcutaneous tissue disorders and abnormal laboratory values, such as decreased WBC count (5/49, 10.20%), decreased neutrophil count (3/49, 6.12%), elevated monocyte percentage (1/49, 2.04%), decreased lymphocyte count (1/49, 2.04%), erythema (1/49, 2.04%), erythra (1/49, 2.04%), and pruritus (1/49, 2.04%). In the groups treated with levornidazole disodium phosphate, gastrointestinal disorders occurred more frequently than in Group C, including nausea (3/46, 6.52%); diarrhea (2/46, 4.35%); and abdominal discomfort, abdominal pain, and vomiting in 2.17% (1/46).

4. Discussion

PID mostly occurs among sexually active women and is mainly caused by poor sexual hygiene, lower genital tract infection, pelvic surgery, and the direct spread of an inflammatory infection from the adjacent organs. According to a recent study on women with PID, gonococcal or chlamydia infection is present in <50% of the women with PID, whereas infection by *M. genitalium*, respiratory pathogens, and bacterial groups related to bacterial vaginosis may account for a large proportion of women with PID[26]. The main intervention for PID includes broad-spectrum antibiotics against *C. trachomatis*, *Neisseria gonorrhoeae*, and anaerobic bacteria[27]. The objectives of PID treatment include eliminating reproductive tract pathogens, resolving clinical signs and symptoms as a short-term goal, and preventing sequelae, such as infertility, ectopic

pregnancy, and chronic pelvic pain, as a long-term goal[9]. Our study suggests that for women with PID, intravenous levornidazole disodium phosphate administered once a day has clinically comparable therapeutic efficacy and safety compared with intravenous levornidazole administered twice a day, although the difference is not significant.

A national multicenter study in China revealed that the common PID-causing pathogens were chlamydia (19.9%), *Ureaplasma urealyticum* or *Mycoplasma hominis* (32.4%), and anaerobic bacteria (25%) and that most cases were mixed infections[6]. An in-depth analysis of the PID Evaluation and Clinical Health (PEACH) study suggested that patients with PID infected with *C. trachomatis* or *M. genitalium* alone had symptoms that lasted significantly longer than those among patients with gonococcal infection or mixed infection before seeking medical treatment[28]. Therefore, when diagnosing and treating PID, clinicians not only need to correct acute symptoms but also need to pay attention to subclinical infection symptoms to prevent serious complications to the greatest extent. After PID is clinically diagnosed, treatment may be initiated without waiting for the results of pathogen examination to avoid the adverse consequences of treatment delay[1].

In the recent years, guidelines for the diagnosis and treatment of PID among countries have included the same principles of antibiotic use, and the vast majority of regimens include antibiotic combination treatment. However, there are some differences in terms of the recommended medication, with metronidazole administered as an intravenous infusion or as a multiroute regimen[1,12,13,29]. Levornidazole is widely used as an alternative to metronidazole; levornidazole diphosphate is a third-generation nitroimidazole antibacterial agent and a national class of antimicrobials. Pharmacokinetic studies on levornidazole disodium phosphate have demonstrated the rapid metabolism to levononazole after administration, and the pharmacokinetic profile of levononazole, the major metabolite, is generally consistent with that of levononazole when administered equimolarly. In addition, the organismal exposure of levononazole increases in proportion to the dose administered, indicating that levornidazole disodium phosphate is a concentration-dependent antibiotic[30]. Disodium levornidazole phosphate injection was shown to be well tolerated by healthy Chinese subjects after multiple-dose administration (0.5 g twice a day and 1.0 g once a day) in a multiple-dose trial, and the safety and tolerability of the 1.0 g dosage was superior than the other[31]. This finding is consistent with those of our study. Levornidazole disodium phosphate therapy was found to be clinically comparable with levornidazole therapy (cure rates of 77.55%, 83.67%, and 82.61% in Groups A, B, and C, respectively), whereas the occurrence of drug-related adverse events was significantly lower in Groups B and C than in Group A.

Several limitations of this study should be acknowledged. First, the pathogen detection rate was low: only 29.17% (42/144) of all patients had positive bacterial cultures at baseline. Depending on the analysis population (FAS *vs*. PPS), the number of microbiologically valid cases ranged from 38 to 42. This limited sample size may reduce the statistical power of the bacteriological efficacy analysis and restrict the interpretation of microbiological outcomes. Second, all patients received the same oral sequential regimen (levofloxacin+ornidazole) after 7 days of intravenous treatment. Therefore, the clinical and bacteriological efficacy observed during days 8-14 may have been influenced by both the intravenous and oral treatment phases, rather than being attributable exclusively to the intravenous study drugs. Third, the present study was designed primarily to evaluate short-term clinical efficacy and safety during the acute treatment phase. Accordingly, long-term reproductive outcomes, including disease recurrence, infertility, ectopic pregnancy, and chronic pelvic pain, were not prespecified study endpoints. As these sequelae are multifactorial and typically require prolonged prospective follow-up for reliable assessment, future studies with extended follow-up durations are warranted to further evaluate long-term reproductive prognosis. Fourth, this study was conducted exclusively in Chinese women, and caution should be exercised when extrapolating these findings to other ethnic populations or geographic regions. Further multinational and multicenter studies are needed to validate the generalizability of the present findings. Finally, endocervical cultures may not fully reflect pathogens located in the upper genital tract in patients with PID. In addition, nucleic acid amplification testing for *Neisseria gonorrhoeae* and *C. trachomatis*, as well as antimicrobial susceptibility testing, were not uniformly implemented across all participating centers as part of routine microbiological assessment, which may have affected the comprehensiveness of pathogen evaluation.

Levornidazole disodium phosphate therapy was found to be clinically comparable with levornidazole therapy in terms of the criteria of clinical efficacy, bacteriological efficacy, and comprehensive efficacy, although the former was associated with significantly fewer drug-related adverse events. Thus, our study suggests that 1.0 g of levornidazole disodium phosphate once a day or 0.5 g twice a day is an effective therapeutic option for patients with PID and that the treatment course should span 14 days.

Conflict of interest statement

YW, SJ and RW were from Yangtze River Pharmaceutical Group Co, Ltd.. The other authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was conducted according to the Declaration of Helsinki and ethical approval was granted by the First Affiliated Hospital with Nanjing Medical University Medical Ethics Committee (Approval No. 2017-SR-014). Written informed consent was obtained from participants.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

YW and RW contributed to study design and drafting of the manuscript. SJ, ZY and LZ contributed to data collection. ZF, XJ and MX contributed to statistical analysis. YL and JK contributed to editing of the manuscript. All authors have read and approved the final manuscript.

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Supplementary Table 1. Positive bacterial culture before medication.

	Group A	Group B	Group C	Total	Statistics	*P*-value
Patients	49	49	46	144	Probability	0.2327
Postive(%)	17(34.69)	16(32.65)	9(19.57)	42(29.17%)		
Peptoniphilus asaccharolyticus	2	1	0	3		
P.asaccharolyticus	1	0	0	1		
Prevotella melaninogenica	1	1	0	2		
Clostridium perfringen	0	1	0	1		
B.fragilis	0	2	1	3		
Finegoldiamagna	2	1	1	4		
Prevotella bivia	5	5	3	13		
Lactobacillus fermentum	0	1	0	1		
Prevotella disiens	1	1	0	2		
Prevotella oralis	0	0	1	1		
Actinomyces naeslundii	0	2	0	2		
Anaerobic coccus Prevotella	1	0	1	2		
Bifidobacterium	1	1	0	2		
Micrococcus tetragenus	0	1	0	1		
Veillonella	2	3	1	6		
P.anaerobius	2	2	1	5		
Vaginal anaerococcus spp	2	0	0	2		
Total	20	22	9	51		

Supplementary Table 2. Fourteen-day comprehensive efficacy (mFAS).

	Group A	Group B	Group C	*P*-value
n	17	16	9	0.295
Cure, n (%)	11 (64.71)	14 (87.5)	8 (88.89)	
95% CI	(38.33, 85.79)	(61.65, 98.45)	(51.75, 99.72)	
Group comparation	A-B	B-C	A-C	
Rate difference	-22.79	-1.39	-24.18	
95% CI	(-54.29, 9.89)	(-40.95, 37.93)	(-60.01, 17.84)	

Supplementary Table 3. Adverse events occurring in ≥5% of participants in any treatment group (SOC and PT levels).

System organ class (SOC)	Preferred term (PT)	Group A (n=49), n (%)	Group B (n=49), n (%)	Group C (n=46), n (%)	P value	Cutoff threshold
Gastrointestinal disorders	Overall SOC	8 (16.33)	6 (12.24)	7 (15.22)	0.8747	≥15%
	Abdominal pain	5 (10.20)	0 (0.00)	1 (2.17)	0.0311	≥10%
	Diarrhoea	0 (0.00)	0 (0.00)	4 (8.70)	0.0095	≥5%
	Nausea	1 (2.04)	1 (2.04)	3 (6.52)	0.4471	≥5%
Skin and subcutaneous tissue disorders	Overall SOC	3 (6.12)	3 (6.12)	7 (15.22)	0.2205	≥15%
	Pruritus	3 (6.12)	2 (4.08)	6 (13.04)	0.2757	≥10%
Infections and infestations	Overall SOC	7 (14.29)	7 (14.29)	2 (4.35)	0.2077	≥10%
Investigations	Overall SOC	7 (14.29)	3 (6.12)	5 (10.87)	0.4083	≥10%
	White blood cell count decreased	5 (10.20)	1 (2.04)	3 (6.52)	0.242	≥10%
	Neutrophil count decreased	3 (6.12)	1 (2.04)	0 (0.00)	0.3245	≥5%
Nervous system disorders	Overall SOC	6 (12.24)	1 (2.04)	4 (8.70)	0.1579	≥10%
	Dizziness	4 (8.16)	0 (0.00)	4 (8.70)	0.0983	≥5%
General disorders and administration site conditions	Overall SOC	4 (8.16)	4 (8.16)	5 (10.87)	0.8747	≥10%
	Fatigue	0 (0.00)	0 (0.00)	3 (6.52)	0.0311	≥5%
Musculoskeletal and connective tissue disorders	Overall SOC	2 (4.08)	5 (10.20)	1 (2.17)	0.2771	≥10%
Reproductive system and breast disorders	Overall SOC	1 (2.04)	5 (10.20)	1 (2.17)	0.2167	≥10%
Blood and lymphatic system	Overall SOC	3 (6.12)	0 (0.00)	1 (2.17)	—	≥5%

System organ class (SOC)	Preferred term (PT)	Group A (n=49), n (%)	Group B (n=49), n (%)	Group C (n=46), n (%)	P value	Cutoff threshold
disorders						
	Anaemia	3 (6.12)	0 (0.00)	1 (2.17)	0.2194	≥5%

Note: Values are presented as number of participants (%). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Bold values indicate events occurring in ≥5% of participants in at least one treatment group. SOC-level summaries represent the number of participants with at least one event within the corresponding SOC; therefore, SOC and PT counts are not mutually exclusive. P values were calculated using the χ^2 test or Fisher's exact test, as appropriate.