The efficacy, safety, and tolerability of levofloxacin quadruple therapy for helicobacter pylori eradication: a randomized, double-blind clinical trial

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Abstract

Background

The incidence of microbial resistance is increasing, and new rescue regimens are needed in order to treat *Helicobacter pylori* (*H. pylori*) infection. To evaluate the efficacy, safety, and tolerability of levofloxacin based quadruple therapies in the eradication of *H. pylori*.

Methods

In a randomized, double-blind clinical trial, 220 patients with dyspepsia and *H. pylori* infection were randomly assigned to receive either bismuth subcitrate 240 mg, pantoprazole 20 mg, amoxicillin 1000 mg twice a day, and levofloxacin 500 mg daily for seven days (BPAL-7), or ten days (BPAL-10). The eradication of *H. pylori* was evaluated two months after the end of treatment, and adverse drug reactions (ADRs) were assessed during the intervention.

Results

According to intention-to-treat and per-protocol, the eradication rate was significantly lower in the BPAL-7 regimen 49.1% (95% CI: 39.3–57.8) and 47.6% (95% CI: 39.7–58.4), respectively compared to the BPAL-10 regimen 62.7% (95% CI: 53.6–72.8) and 62.4% (95% CI: 55.1–72.8), respectively. The incidence of ADRs was not statistically significant between BPAL-7 (33.6%) and BPAL-10 (36.7%) groups.

Conclusion

Although the ADRs were negligible in both groups, these regimens could not be an ideal alternative therapy for *H. pylori* because of low eradication rates compared to standard regimens.

Trial registration: The study reviewed and approved by the Iranian Registry of Clinical Trials (IRCT201406141155N19). This trial was retrospectively registered on July 10, 2015.

Background

Helicobacter pylori (*H. pylori*) affects about 80% of the total population in developing countries and 20–50% in developed countries. The infection as a worldwide health problem is associated with acute and chronic gastritis, peptic ulcer disease, and gastric cancer [1–3]. The eradication of *H. pylori* has a main role in the prevention and treatment of these complications [4, 5]. However, the major concerns of *H. pylori* treatment are low patients compliance, adverse drug reactions (ADRs), and microbial resistance to medicines [6, 7].

The efficacy of present pharmacological treatments for *H. pylori* infection has evaluated in different studies [8–14]. The co-administration of a proton-pump inhibitor (PPI) and two antibiotics (triple therapy), or addition of bismuth salts to the triple therapy (bismuth-based quadruple therapy) for a period of 14

days are the most common regimens [15]. Among antibacterial agents, amoxicillin or metronidazole, along with clarithromycin, are the first-line treatment for eradication of *H. pylori* [9, 16]. Nevertheless, microbial resistance is one of the challenging factors of treatment, which causes low efficacy of these regimens. Hence, effective antibiotics should be selected according to the regional pattern of *H. pylori* resistance [17, 18].

The prevalence of *H. pylori* infection is relatively high among the Iranian population [19, 20]. Moreover, novel strains resisted to clarithromycin and metronidazole are prevalent in some geographical part of Iran [21, 22]. Therefore, a body of evidence suggested new antibiotic regimens with higher efficacy (eradication rate of > 80%), lower ADRs and cost, and acceptable patient compliance. The efficacy of levofloxacin as a new-generation quinolone in the treatment of *H. pylori* infection has assessed in several studies, and levofloxacin-containing regimens have shown various eradication rates [23–29].

The current study aimed to evaluate the efficacy, safety, and tolerability of seven- and ten-day period of bismuth subcitrate, pantoprazole, amoxicillin, and levofloxacin regimens in the eradication of *H. pylori* among patients referred to Gastrointestinal Outpatient Clinic of Razi hospital, Rasht, Iran.

Methods

Trial design

This study was a phase III open-label, randomized, double-blind controlled trial carried out between July 2015 to November 2015 at Gastrointestinal and Liver Diseases Research Center (GLDRC), Rasht, Iran. All included participants were randomly divided into one of the therapeutic regimens and signed informed consent. The eradication rate of *H. pylori* was assessed two months after the end of the intervention, and the incidence of ADRs and patient compliance were at the end of treatment.

Ethical consideration

The protocol of the study was approved by the local ethical committee of Guilan University of Medical Sciences (Ethics committee code; 1930175713), and also performed according to the declaration of Helsinki for human subjects. The study reviewed and approved by the Iranian Registry of Clinical Trials (IRCT201406141155N19).

Patients

Patients complaining of dyspeptic symptoms referred to the Gastrointestinal Outpatient Clinic of Razi hospital, Rasht, Iran, were enrolled. The main inclusion criteria were a positive rapid urease test and 15 to 65 years of age. Patients with coexisting serious illnesses, including liver cirrhosis, renal failure, heart failure, gastrointestinal malignancies, and history of seizure or hematologic diseases, allergy to medications, and previous incomplete treatment course as well as pregnant or nursing mothers were excluded.

Randomization and intervention

A block randomization method was used in order to assign patients randomly into permuted treatment blocks and ensure equal numbers in each group of treatment. One of these groups received a seven-day period of bismuth subcitrate 240 mg, pantoprazole 20 mg, amoxicillin 1000 mg twice a day, and levofloxacin 500 mg daily (BPAL-7), and the other received a ten-day period of the same regimen (BPAL-10).

Patients were recommended to take bismuth subcitrate, pantoprazole, and levofloxacin before meals, and amoxicillin after meals at the scheduled times. It also advised avoiding smoking, drinking alcoholic or caffeinated beverages, eating spicy foods, and taking non-steroidal anti-inflammatory drugs or medications containing a monoamine oxidize inhibitor.

Demographic criteria, including age, gender, cigarette smoking, and alcohol drinking, were recorded.

Evaluation of H. pylori eradication

Two months after the end of the intervention, a Heliprobe ^{14}C-Urea Breath Test (^{14}C-UBT, Kibion AB, Uppsala, Sweden) with a 95% sensitivity and 100% specificity was performed to evaluate the *H. pylori* eradication. The treatment success was defined as the result of < 50 disintegrations per minute (DPM). Taking the medicines were stopped during these two months to avoid interaction with the results of ^{14}C-UBT.

Assessment of ADRs and patient compliance

All patients were informed about potential ADRs, including pyrosis, anorexia, nausea, vomiting, bitter taste, abdominal colic, epigastric pain, headache, and back pain. The ADRs were evaluated during the intervention, using a 0–10 scoring system (mild: 0–3, the ADRs exist but insufferable; moderate: 4–6, ADRs sometimes interfere daily life activity; severe: 7–10, ADRs interfere continuously with daily life activities). Acceptable patient compliance was defined as consumption of > 80% of the prescribed medicines [30].

Statistical analyses

The eradication rate of two regimens was determined using Intention-to-treat (ITT) and per-protocol (PP) analysis. Patients declined to proceed with the treatment, or those with poor compliance were excluded from PP analysis; however, all patients, including patients who used the treatments out of the protocols or dropouts were included in ITT analysis. The eradication rate of *H. pylori*, odd ratios, and 95% confidence interval were evaluated for each regimen. Chi-square and *t* tests were employed to compare qualitative and quantitative variables between two treatment groups, respectively. All statistical analyses were performed using SPSS, version 18.0 software (SPSS Inc, Chicago, IL, United States). A $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients

A total of 220 patients with *H. pylori* infection were randomly assigned to either BPAL-7 (n = 110) or BPAL-10 (n = 110) groups. Three patients in the BPAL-7 group (one female with severe epigastric pain and diarrhea, and two males with severe anorexia and back pain) and one patient in the BPAL-10 group (one female with severe epigastric pain and nausea) were excluded from the trial because of drug intolerance and low compliance. A flow diagram describing patient selection and study outcomes is shown in Fig. 1.

No significant differences were observed between the two groups in terms of age, gender, cigarette smoking, alcohol drinking (P > 0.05). The Basic demographic characteristics of the patients are demonstrated in Table 1.

Table 1
Demographic characteristics of the study patients

Characteristics	**BPAL-7 regimen (n = 107)**	**BPAL-10 regimen (n = 109)**	***P* value**
Gender, male	39 (36.5)	40 (36.7)	0.888
Age	41.46 ± 13.25	44.16 ± 12.70	0.649
Cigarette smoking	4 (3.7)	7 (6.4)	0.353
Yes	103 (96.3)	102 (93.6)	
No			
Alcohol drinking	1 (0.9)	3 (2.7)	0.313
Yes	106 (99.1)	106 (97.3)	
No			
Values were demonstrated as numbers (percentages) and Mean ± SD for categorical and continuous variables, respectively.			
Chi-square and *t* tests were performed to compare categorical and continuous variables between groups, respectively.			
BPAL-7 and BPAL-10; bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.			

Eradication rates

The eradication rate of BPAL-7 regimen (49.1%, 95% CI: 39.3–57.8) was lower than that of BPAL-10 regimen (62.7%, 95% CI: 53.6–72.8) on ITT analysis (OR = 1.75, P < 0.05). Additionally, PP analysis also demonstrated a lower eradication rate in BPAL-7 regimen (47.6%, 95% CI: 39.7–58.4) compared to that of BPAL-10 regimen (62.4%, 95% CI: 55.1–72.8) (OR = 0.54, P < 0.05). The eradication rates of the two regimens are represented in Table 2. Univariate analyses were shown no association between age, gender, cigarette smoking, and alcohol drinking with an eradication rate of *H. pylori* in both groups (P > 0.05).

Table 2
The eradication rates of the BPAL-7 and BPAL-10 regimens.

Analyses	BPAL-7 regimen (n = 107)	BPAL-10 regimen (n = 109)	*P* value
Intention-to-treat	54 (49.1)	69 (62.7)	0.037
Per-protocol	51 (47.6)	68 (62.4)	0.024
Values were demonstrated as numbers (percentages).			
^{14}C-urea breath test was conducted to confirm the eradication of *H. pylori* two months after the end of treatment.			
Chi-square test was performed to compare variables between groups.			
BPAL-7 and BPAL-10; bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.			

ADRs and patient compliances

Both BPAL-7 and PBAL-10 regimens were well-tolerated by a majority of patients. The number of patients with ADRs was not statistically significant between the BPAL-7 group (36 patients, 33.6%) and the BPAL-10 group (40 patients, 36.7%). ADRs were rated as mild (55 patients, 25%), moderate (17 patients, 7.7%), and severe (4 patients, 1.8%). The most-reported ADRs were epigastric pain, nausea, vomiting, and bitter taste in both regimens (Table 3).

Table 3
The adverse drug reactions associated with the BPAL-7 and BPAL-10 regimens.

ADRs	BPAL-7 (n = 107)			BPAL-10 (n = 109)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Pyrosis	31 (29.0)	4 (3.7)	1 (0.9)	23 (21.1)	10 (9.2)	1 (0.9)
Anorexia	25 (23.4)	4 (3.7)	2 (1.9)	21 (19.3)	4 (3.7)	1 (0.9)
Nausea	19 (17.8)	2 (1.8)	1 (0.9)	25 (22.9)	0 (0.0)	0 (0.0)
Vomiting	2 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Bitter taste	19 (17.8)	0 (0.0)	1 (0.9)	10 (9.2)	2 (1.8)	1 (0.9)
Abdominal colic	12 (11.2)	0 (0.0)	0 (0.0)	9 (8.2)	3 (2.7)	0 (0.0)
Epigastric pain	17 (15.9)	7 (6.5)	1 (0.9)	22 (20.2)	3 (2.7)	1 (0.9)
Headache	15 (14.0)	2 (1.9)	1 (0.9)	16 (14.7)	7 (6.4)	1 (0.9)
Back pain	6 (5.6)	1 (0.9)	2 (1.9)	9 (8.3)	6 (5.5)	1 (0.9)
Values were demonstrated as numbers (percentages).						
Adverse drug reactions were evaluated during the study.						
Chi-square test was performed to compare variables between groups. None of variables were shown statistically significant differences between two regimens in each category.						
ADRs; adverse drug reactions, BPAL-7 and BPAL-10; bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.						

The compliance rates were 97.3% and 99.1% for the BPAL-7 and PBAL-10 regimens, respectively. Three patients in the BPAL-7 regimen and one patient in the PBAL-10 regimen excluded from the PP analysis because of failure to ingest > 80% of the medications.

Discussion

The finding of the present study showed a lower rate of *H. pylori* eradication in the BPAL-7 regimen compared to the BPAL-10 regimen among patients with dyspepsia and *H. pylori* infection. Both BPAL-7 and PBAL-10 regimens were well-tolerated and had acceptable patient compliance.

Recent guidelines suggest the eradication rate of triple therapy with a PPI, amoxicillin or metronidazole, and clarithromycin as first-line regimens have decreased, particularly due to an increase in microbial resistance to clarithromycin [1]. Moreover, some recommended bismuth-based quadruple therapy regimens also have an eradication rate of less than 80% [31]. Therefore, more effective regimens are needed to eradicate the *H. pylori* infection.

A body of evidence suggested to using levofloxacin, a new generation fluoroquinolone with in vitro anti-*H. pylori* activity, as an alternative agent in clarithromycin-resistant cases. Levofloxacin containing triple, quadruple, and sequential regimens have demonstrated a various range of eradication rates [32–34].

A study compared a triple therapy consisting of esomeprazole, levofloxacin (500 mg daily), and amoxicillin with a standard regimen consist of esomeprazole, metronidazole, bismuth, and tetracycline for a period of 14 days. The eradication rate of levofloxacin containing regimen (96.3%) was higher than the standard regimen (86.0%) in ITT analysis [24].

Gisbert *et al.* from Spain demonstrated the eradication rate of ranitidine bismuth citrate, levofloxacin, and amoxicillin as first-line triple therapy for *H. pylori* was 84.4 and ADRs, mainly including diarrhea, were reported in 9.5% of the patients [35]. This group carried out a trial with 1000 patients on the efficacy of omeprazole, levofloxacin, and amoxicillin for ten days. They reported an eradication rate of 73.8% and ADRs of 20%, which most commonly included nausea, metallic taste, and abdominal pain [25]. The dosage of levofloxacin was higher in these studies (500 mg twice a day). In a recent multicenter study conducted by Gisbert *et al.*, 14 days treatment by esomeprazole, amoxicillin, levofloxacin (500 mg daily), and bismuth as a rescue therapy achieved more than 90% of eradiation rate [26]. In another Spanish study, the eradication rate of omeprazole, levofloxacin (500 mg twice a day), and amoxicillin combination for a ten-day period also had about 20% failure rate [36].

A study from Kosovo randomized 105 patients to either seven or ten days levofloxacin-based regimens, including omeprazole, levofloxacin (500 mg daily), and amoxicillin. The eradication rates were 86.2% and 93.6%, respectively. About 5% of patients experienced ADRs, mostly nausea and diarrhea [27].

Several Taiwanese studies evaluated the efficacy of levofloxacin-containing regimens as rescue therapy for the eradication of *H. pylori*. Kuo *et al.* reported the eradication rate of esomeprazole, amoxicillin, and levofloxacin (500 mg daily) regimen for seven days is similar to a second line quadruple standard regimens (about 60–70%) [37]. Four years later, the same group published a study comparing a levofloxacin-containing quadruple therapy (esomeprazole, bismuth, tetracycline, and 500 mg of levofloxacin once daily) for ten days with high-dose metronidazole- containing standard quadruple regimen. Based on their findings, eradication rates of about 80% was reached for both regimens [38]. On the other hand, Hsu *et al.* showed a ten-day quadruple therapy consist of esomeprazole, bismuth, tetracycline, and levofloxacin (500 mg daily) achieved a very high eradication rate (95.8%) at this geographical area. ADRs were detected in 25.0% of patients [39]. In another study, the efficacy of adding bismuth to a levofloxacin-based triple regimen (rabeprazole, bismuth, amoxicillin, and 500 mg of levofloxacin daily) assessed. The results revealed no further significant eradication rat (67.6%), but no more ADRs were noted [40].

According to the results of the present study, the BPAL-7 and the PBAL-10 regimens were not clinically successful in the treatment of *H. pylori* with an eradication rate of 62.7% and 49.1% by ITT analyses, respectively. Both regimens achieved neither cut point of an ideal regimen (eradication rate of > 90%), nor acceptable eradication rate of Maastricht and other guidelines (> 80%) [41]. The low efficacy of these

regimens is likely related to the regional pattern of bacterial resistance. The results of these regimens are consistent with a previous Iranian study evaluating the efficacy of a 14-day triple therapy, comprised of omeprazole, levofloxacin (500 mg daily), amoxicillin with success rate of 75% [42]. However, studies conducted in other parts of Iran revealed fluoroquinolone-containing regimens including a 14-day of omeprazole, levofloxacin (250 mg twice a day) and amoxicillin as well as a 14-day of omeprazole, levofloxacin (500 mg twice a day), and amoxicillin as rescue therapies of *H. pylori* had eradication rate of 90% and 86.7%, respectively [43, 44]. Moreover, there are some other Iranian investigations that evaluated the efficacy of levofloxacin-based, sequential therapy in the treatment of *H. pylori*, and the eradication rate ranged from 70.8% to 85.1% [45–47].

No relationship was observed between patient demographic characteristics including age, gender, cigarette smoking, and alcohol drinking and the success rate of both BPAL-7 and PBAL-10 regimens. Previous studies have also demonstrated the eradication rate of levofloxacin-containing regimens was not associated with age [45, 47, 44], gender [46, 45, 44], smoking status [48, 45], and education level [45].

Although high efficacy along with compatibility with the pattern of regional bacterial resistance are the main properties of an ideal pharmacological regimen for eradication of *H. pylori*, tolerability, patient compliance, simplicity, and cost-efficacy should not be neglected [30]. The compliance rates for the BPAL-7 and PBAL-10 regimens were 97.3% and 99.1%, respectively. In spite of high compliance rats, ADRs were reported in one-third of patients. The most-reported ADRs were epigastric pain, nausea, vomiting, and bitter taste. Generally, BPAL-7 and PBAL-10 regimens were patient compatible and well-tolerated.

Limitations

The main limitations of the present study are the lack of regional pattern of antibiotic resistance and a local estimate of *H. pylori* eradication rate as well as the small number of patients in the groups. The absence of pretreatment susceptibility assessment to levofloxacin is another drawback. Moreover, the finding may not be applicable to patients with previous treatment failure and recurrence disease.

Conclusion

The BPAL-7 and PBAL-10 regimens were patient compatible and well-tolerated. However, both regimens showed no satisfied eradication rate. Therefore, these regimens could not be ideal alternative therapies for *H. pylori* eradication in this region. It is better to evaluate the efficacy and tolerability of this regimen in other geographical regions, longer studies with more sample size.

Abbreviations

H. pylori: *Helicobacter pylori*; **ADRs**:adverse drug reactions; **PPI**:proton-pump inhibitor; **ITT**; intention-to-treat, **PP**; per-protocol, **BPAL-7**:bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven days; **BPAL-10**; bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for ten days

Declarations

Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants provided their written informed consent to participate in this study. For participants under 16 years of age, the consent form was completed by the parents. The study protocol was approved by Ethics Committee of Guilan University of Medical Sciences, Rasht, Iran.

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest in this work.

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Authors' contribution

FJ and FMG designed and supervised the procedure of the research. **FMG**, **MA, HS**, and **BM** enrolled participants, collected data. **FJ**, **SH**, and **MS** analyzed data, and **MF**, **FJ**, **MA, AMG** and **MS** drafted the manuscript. **MF, AMG** and **MA** edited and revised the manuscript. **All authors** have read and approved the final draft of the paper.

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Figures

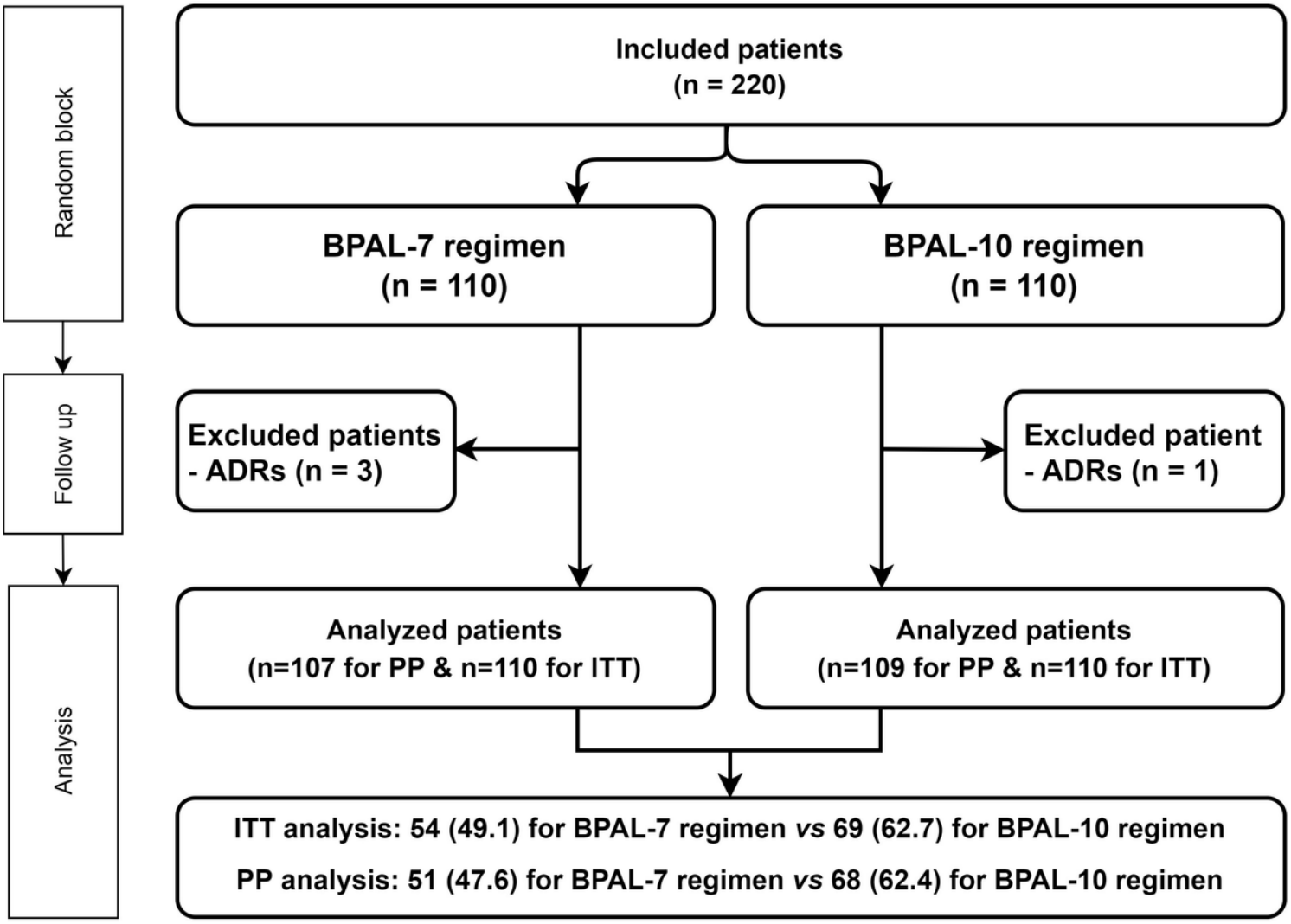

Figure 1

Flow chart for process of patient randomization. ITT; intention-to-treat, PP; per-protocol, ADRs; adverse drug reactions, BPAL-7 and BPAL-10; bismuth-based quadruple therapy containing pantoprazole, amoxicillin, and levofloxacin for seven and ten days, respectively.

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