Study protocol and Statistical Analysis Plan

Optimized bismuth quadruple therapy vs triple standard therapy for Helicobacter pylori eradication:

Clinical efficacy randomized trial.

NCT: Not yet assigned

2022-11-10

Optimized bismuth quadruple therapy vs triple standard therapy for Helicobacter pylori eradication: Clinical efficacy randomized trial.

Introduction

Background and rationale

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a Gram (-) and micro aerophilic bacterium that is uniquely adapted to infect the luminary surface of the gastric epithelium. Although an innate and adaptive immune response to infection is elicited by the host, it is insufficient for bacterial eradication. Therefore, a chronic infection is developed and can persist for decades if no treatment is performed (1).

H. pylori was first identified by Warren and Marshall in 1982. At the time the scientific community doubted any bacteria could survive he acid of the stomach. Marshall ingested the bacterial culture, showing symptoms of the infection. Administration of antibiotics resolved those symptoms fulfilling Koch's postulates, thus demonstrating the pathogenic role of *H. pylori* in peptic ulcer (1).

H. pylori survives the adverse conditions of the stomach by converting urea to ammonium and carbon dioxide changing local pH. In addition, its helical shape and flagellum helps penetrate the mucous layer allowing it to evade the acidic pH of the gastric lumen (1).

H. pylori Infection Epidemiology

H. pylori infection is asymptomatic in most of its carriers; however, a proportion of people will develop:

1. Duodenal or gastric ulcers (1.0% to 10.0%).
2. Gastric cancer (0.1% to 3.0%).
3. MALT (mucosa-associated lymphoid tissue) lymphoma (<0.01%).

H. pylori infection is considered to be one of the main risk factors for the development of gastric adenocarcinoma. For this reason, the International Agency for Research on Cancer (IARC) classified it as a human carcinogen type 1 (2).

The prevalence of *H. pylori* worldwide is estimated to be 48.5%. However, the infection geographical distribution is heterogeneous. Developed countries such as Switzerland (18.9%), Denmark (22.1%), New Zealand (24.0%), Australia (24.6%) and Sweden (26.2%) have low prevalence, close to 20.0% while a a prevalence exceeding 80.0%, in countries such as Nigeria (87.7%), Portugal (86.4%), Estonia (82.5%)) and Pakistan (81.0%) have been described (3)."

Latin America has a high burden of *H. pylori* infection and its associated outcomes., particularly gastric cancer (4). In Chile, Ferreccio et. al., showed that according to the 2003 National Health Survey the prevalence of *H. pylori* infection was 73.0% (95%CI: 70.0%-76.0%). Maximum values were found between in the 45 to 64 years old group with a decrease at older ages. In addition, men were significantly more infected (5). Considering the reports published in the decade of 2000-2010, Chile has one of the highest prevalences worldwide and within Latin America, reaching more than 70.0% (3).

During 2020, In Chile gastric cancer was the second leading cause of cancer deaths (second in men and fourth in women) (6). From 1985 to 2002, gastric cancer mortality rate was 19.2 per 100,000 population (7). The incidence and mortality rate of gastric cancer has remained unchanged over the past 20 years, despite strategies developed to try to reduce its incidence. In addition, the Chilean Ministry of Health estimated in 2013, 34,700 Years of Potential Lost years of life due to the infection (8). In parallel, GLOBOCAN reports that there has been an increase in the incidence of stomach cancer in people under 50 years of age in Chile (9).

Role of *H. pylori* eradication in Public Health

Successful eradication of H pylori has been shown to prevent its associated outcomes, including gastric cancer, with an RR of 0.6 (95% CI: 0.4-0.9) with a relative decrease in risk of 40.0% when comparing those eradicated versus non-eradicated (4, 10).

The preventive effect of eradication has better performance when used in patients who have not developed cancer yet but show early preneoplastic histological alterations giving the chance to the gastric mucosa to return to normal after eradication (10). Therefore, the Maastricht consensus recommends addressing H pylori infection with a preventive approach of *testing and treating*[1] in people with dyspepsia without diagnosis, especially in those areas with high prevalence of infection (10). The Taipei consensus makes its recommendations along the same lines, recommending the strategy of testing and treating young adults who belong to populations with a high incidence of gastric cancer, before atrophic gastritis

[1] It involves testing for *H. pylori* through a non-invasive method in patients with dyspepsia and performing eradication therapy in those patients positive to the infection.

and intestinal metaplasia develop (11). A recent study in the Matsu Islands where this type of strategy was implemented showed a decrease in *H. pylori* infection rates from 64.2% to 15.0%, with reinfection rates lower than 1% per person-year. During the 1995 to 2003 period, the effectiveness of this intervention strategy reduced the incidence of gastric cancer to 53.0% (95% CI: 30% to 69%) (12).

Eradication schemes and their effectiveness

Currently, in Chile, patients with peptic ulcer disease and *H. pylori* infection are beneficiaries of free eradication through the Explicit Health Guarantees program. [2] The clinical practice guidelines for *Helicobacter pylori* eradication therapy in patient with peptic ulcer disease recommends as first-line therapy:

1. A standard dose of proton pump inhibitor, every 12 hours
2. Clarithromycin, 500 mg every 12 hours orally.
3. Amoxicillin 1 gr every 12 hours orally. Metronidazole 500 mg is used every 12 hours in case of penicillin allergy.

This scheme constitutes the standard triple therapy (OAC triple therapy), and is administered for 14 days (14). This eradication scheme has been widely recommended as a primary therapy in populations with low CLA resistance, with expected success rates of 80.0% to 85.0% (10). This therapeutic scheme effectiveness is supported in Latin America by a study demonstrating 82.2% (95% CI = 78.5%-85.5%) of eradication when compared with concomitant 5-day therapy and 10 days sequential therapy schemes (15)..

In Latin America, a multicenter trial of 1463 participants from Chile, Colombia, Costa Rica, Honduras, Nicaragua and Mexico reported an eradication rate for triple therapy of 82.2% in post-treatment control which dropped to 80.4% at the one year follow-up , which is on the verge of the accepted therapeutical efficacy limits (>80%) (4).

The effectiveness of the OAC scheme has shown a clear downward trend, with eradication rates falling below 80.0% in *intention-to-treat* analyses. An increase in antibiotic resistance (4), the limited amount of

[2] In agreement with the *MEDICAL AND ADMINISTRATIVE TECHNICAL STANDARDS FOR COMPLIANCE WITH THE EXPLICIT HEALTH GUARANTEES OF LAW 19.966*. The inclusion criteria for Eradication treatment is all people with *Helicobacter pylori* positive plus any of the following conditions: to be over 40 years of age, to have confirmed gastric or duodenal ulcer, MALT lymphoma, atrophic gastritis, first-degree relatives with a history of gastric cancer, having gastric resection for gastric cancer, dysfunctional dyspepsia 13. MINSAL. APPROVED STANDARDS OF A MEDICAL AND ADMINISTRATIVE TECHNICAL NATURE FOR COMPLIANCE WITH THE EXPLICIT HEALTH GUARANTEES OF LAW 19,966. In: PUBLIC SDS, editor. 2013..

antibiotics that have shown effectiveness for H. pylori treatment and the extensive use of some of them in other infectious diseases (clarithromycin use in respiratory infections) are mostly to blame (16).

Antibiotic resistance mechanisms of are mostly chromosome encoded mutations, changes in the bacterial physiology leading to decrease in the entry and increase on excretion of these of antibiotics or from the bacteria, and the creation of biofilms or cocoid-like bacterial colonies. Through these mechanisms, *H. pylori* strains can manifest three antibiotic resistance profiles: single antibiotic resistance, multi-resistance, and hetero-resistance (16).

Another variable identified as a barrier in the effectiveness of eradication therapy is the influence of polymorphisms on CYP2C19 cytochrome. These polymorphisms affect the metabolization of most PPIs. resulting in several haplotypes of metabolizers (homozygous and heterozygous rapid metabolizers or slow metabolizers). Rapid metabolizers show a decreased effect on PPIs effectiveness, so a limited increase in pH is observed. This can drastically decrease the effectiveness of the eradication therapy, since is a pH between 6 and 7 is necessary for antibiotics optimal effect (17, 18).

In this scenario, international guidelines for the management of *H. pylori* infection recommend avoiding the use of clarithromycin and levofloxacin as first-line therapy when *H. pylori* strains resistance rates in any given population is over 15% (19). Recent studies in Chile report clarithromycin resistance rates up to 26% (20) and 27% (21). For this reason, the use of clarithromycin in Chile as a first-line therapy should be avoided.

in Latin America, studies show low prevalence of resistance (4% (95%CI: 2-8%) for amoxicillin (22). On the contrary high resistance rates for metronidazole have been described 53% (95% CI: 46-60%). Regardless of the fact its use continues since resistance to metronidazole can be overcome with the prolongation of therapy, increasing the dose of the antibiotic or using it concomitantly with bismuth (22)."

Relevance of *H. pylori* eradication therapy schemes analysis in Chile: Study Justification

The high prevalence of *H. pylori* infection in the Chilean population justifies the need for an eradication program that is practical, low-cost and effective.

The latest consensus for the Management of *H. pylori* in Latin America establishes that quadruple therapy between 10 and 14 days should be studied in the region because it can be a good alternative for the eradication of *H. pylori* as a first or second line therapy in areas with high prevalence of resistance to clarithromycin and metronidazole as it is the case in Chile (4, 20-22). The Toronto Consensus for the

Treatment of *H. pylori* Infection in Adults agrees on this point, recommending quadruple bismuth therapy as first-line therapy and that the duration of the treatment be 14 days (19).

in Chile a recent study Reyes et al. analyzed eradication and adverse event rates of the most commonly used *H. pylori* eradication schemes in a retrospective cohort design, based on clinical records of patients treated at 2 health centers in Santiago de Chile (23). **The study reports an eradication rate of 97.62% for quadruple bismuth therapy, versus 81.95% for standard triple therapy**. Despite its promising results, the study has limitations: drug use for each of the therapies was heterogeneous and according to attending physician criteria. Success of *H. pylori* eradication was also defined by the attending physician. Regardless, this study supports the hypothesis that in Chile the use of quadruple bismuth therapy may be the most effective option for the successful eradication of *H. pylori* in its population.

This study proposes a randomized, multicenter, controlled, double-blind clinical trial with two parallel groups with the aim of generating the best possible quality of evidence to justify the use of quadruple bismuth therapy in Chile, and confirm the promising results of the retrospective cohort of Reyes et.al. (23).

Research Question and Hypothesis

Research Question: Is the *quadruple therapy with bismuth* better than the *Standard triple therapy* used in Chile for the eradication of *Helicobacter pylori* in Chilean patients?

Hypothesis: The use of an optimized quadruple therapy with bismuth (intervention) compared to standard triple therapy will increase the rate of *H. pylori* eradication from 80.0% to 95.0% in infected Chilean population

Methods

AIMS

Primary aim

To compare the *H. pylori* eradication rate between the quadruple bismuth therapy versus the standard triple therapy recommended by the AUGE Clinical Guidelines for *Helicobacter pylori* eradication treatment in peptic ulcer patients.

Secondary – exploratory aims

To determine the incidence of Adverse Drug Reactions (ADRs) and the therapeutic adherence to quadruple bismuth therapy versus the standard triple therapy recommended by the AUGE Clinical Guidelines for *Helicobacter pylori* eradication treatment in peptic ulcer patients.

To determine any possible additional factors such as sociodemographic variables, comorbidities, infection with resistant strains and polymorphism of CYP2C19 that may increase or decrease the probability of success of the eradication therapies under study in this particular population setting

Studio Design

Randomized, multicenter, controlled, double-blind clinical trial with two parallel arms. The control group will receive the current *Standard Triple Therapy* for the eradication of *H. pylori*. It consists in omeprazole + amoxicillin + clarithromycin for 14 days. The intervention group will be administered *Quadruple Therapy with Bismuth*, that consists in esomeprazole + amoxicillin + metronidazole + bismuth subsalicylate for 14 days. Details can be found in Table 1.

The proposal follows the CONSORT methodology and criteria for randomized, prospective double-blind clinical studies and will be enrolled in www.clinicaltrials.gov.

Inclusion and exclusion criteria for participants

Inclusion Criteria:

1. Age between 18-75 years
2. Diagnosed with *H. pylori* infection [3]
    a. By positive Urease test.

Exclusion criteria:

1. Pregnant or lactating women.
2. Allergy or history of adverse reaction to the following medications:
    a. Penicillin
    b. Salicylate allergy[4]
    c. Omeprazole
3. Has received H. *pylori* eradication therapy prior to the study.

[3] Less than 1 week between diagnosis time and contact with recruiter
[4] As acetylsalicylic acid

4. Has used PPIs 14 day prior to diagnostic testing
5. Use of antibiotics within 4 weeks beforehand.
6. History of gastrointestinal bleeding for the last 12 weeks.
7. History of partial gastrectomy due to Gastric Cancer
8. History of incipient Gastric Cancer resolved by endoscopic resection.
9. History of bariatric surgery.
10. Serious or malignant diseases with less than 1 year life expectancy.
11. History of *Clostridium difficile infection.*
12. History of inflammatory bowel disease.
13. Chronic kidney disease, stage 3 or higher.
14. Do not sign informed consent.

Context and locations where the data will be collected

Participants will be recruited into the UC-CHRISTUS Health Network located in the City of Santiago de Chile. The recruitment process is projected to last 6 months, during July to December 2022, considering an additional 3 months for eradication confirmation by urea breath test.

Interventions for each group

As previously mentioned, this study compares the Quadruple Therapy with the Standard Triple Therapy, detailed in the Table 1.

Participants who no not achieve infection eradication will be referred to the gastroenterology team. They will be responsible for providing second line treatment under the current standard of care.

Table 1. Description of the intervention and control of the study.

Intervention: Quadruple Therapy	**Control: Standard Triple Therapy**
Esomeprazole 40 mg every 8 hours	Omeprazole 20mg every 12 hours
Amoxicillin 1 gr every 8 hours	Amoxicillin 1 gr every 12 hours
Metronidazole 500 mg every 8 hours	Clarithromycin 500 mg every 12 hours
Bismuth subsalicylate 246 mg, 1.5 tablets, every 8 hours	Placebo identical to Bismuth Subsalicylate, 1.5 Tablets 3 times daily

Primary and secondary outcomes

Primary outcome:

H. pylori Eradication: To determine eradication, participants of these study will be invited 8 to 12 weeks after the end of the administered therapy. Each participant will be given a Urea Breath Test (UBT) for eradication confirmation. This test has been widely validated by all International Consensus and Clinical Guidelines, given its excellent sensitivity, specificity, safety and acceptance by patients[5] (4, 10, 11, 19). If the participant reports antibiotic or proton pump inhibitor use in the last 15 days, appointments will be rescheduled at least for 15 days later. This study will be complemented with a serology test for *H. pylori*, for which a blood sample will be taken at the time of recruitment and during the UBT appointment.

Secondary-exploratory outcomes:

Incidence of *Adverse Drug Reactions* (ADRs): A questionnaire will be performed to determine the occurrence of any adverse effect attributable to the therapy. The incidence of bloating, abdominal pain, bitter taste, constipation, diarrhea, dizziness, dyspepsia, epigastric pain, halitosis, headache, loss of appetite, nausea, vomiting, oral ulcers, skin rashes and drowsiness will be directly recorded. Symptoms reported by participants spontaneously in follow-up phone calls will also be recorded. The time of commencement and duration of the therapy will be recorded.

H. pylori Antibiotic Resistance and Host CYP2C19 polymorphisms determination:

For DNA extraction the same gastric biopsy used for the rapid urease test (Pronto Dry) in endoscopy prior to admission will be used. No additional samples will be taken than those required as part of routine clinical practice. DNA will be extracted the biopsy using the *QIAamp DNA* mini kit (Quiagen) according to the manufacturer's instructions.

To determine the susceptibility to Clarithromycin, PCRs will be performed with specific allele primers (ASP-PCR) for point mutations A2142G and A2143G of the *H. pylori* 23s rRNA gene. Two pairs of primers will be used; the first pair targets a 320 bp fragment of the gene containing the mutation sites and consists of FP-1 5'TCGAAGGTTAAGAGGATGCGTCAGTC3' and RP-1 5'GACTCCATAAGAGCCAAAGCCCTTAC3'; the second

[5] For UBT one capsule of 75 of Urea with isotopic marker of carbon 13 (^{13}C) will be administered with 50 mL of water. After 10 minutes, the participant will be asked to exhale in a bag. The resulting breath sample is analyzed with an infrared mass spectrometry device attached to a computer, which results in:

1. Positive (delta on baseline ≥4%)
2. Negative (delta on baseline <2.5%)
3. Inconclusive: delta values between 2.5% and 4%

pair is composed of the primers targeting the respective mutations, FP2143G 5'CCGCGGCAAGACAGAGA3' and RP2142G 5'AGTAAAGCCACCACGGGGTATTCC3'. For PCR an initial denaturation step will be performed at 95°C for 5 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds, hybridization at 60.5°C for 20 seconds, extension at 68°C for 30 seconds and a final extension for 2 minutes at 68°C. The visualization of the results will be done in a 3% agarose gel. Strains that possessed fragments of 320 bp will be considered as wild type and those that had fragments of 238 bp and 118 bp as strains containing the mutation A2142G and A2143G, respectively.

Different point mutations of the gyrA gene determinant region for quinolone resistance (QRDR) are responsible for conferring resistance to Levofloxacin. ASP-PCR will be performed. Primers are described in TABLE N°x.

Table N°X Primers for detecting LEV resistance in the gyrA gene

Primer	Sequence (5'→3')	Mutation
F261A1	CCCCCATGGCGAGAAAG	C261A
F261G1	CCCCCATGGCGAGAAGG	C261G
F271A5	GCGATAACGCGGTTTAGAA	C271A
F271A9	GCGATAATGCGGTTTAGAA	G271A
F271T9	GGCGATAATGCGGTTAATTA	G271T
F272G1	GCGATAACGCGGTTTAGGGT	A272G
F272G9	GCGATAATGCGGTTTAGGGT	A272G
F87ATC	CCCCCATGGCGAGATCG	A260T, T261C
gyrA R	GTTAGGCAGACGGCTTGGTARAATA	C261A

For PCR an initial denaturation will be performed at 94°C for 2 minutes, followed by 40 cycles of denaturation at 98°C for 10 seconds, hybridization at 65°C for 30 seconds, extension at 68°C for 20 seconds and a final extension for 2 minutes at 68°C. The visualization of the results will be done in a 2% agarose

gel. Strains with fragments of 428 bp will be considered as wild type and those who show a fragment of 254 bp will be considered as resistant to LEV mutants.

For Amoxicillin and Metronidazole resistance PCR amplification of fragments of interest for the pbp-1 and rdxA/frxA resistance genes respectively will be performed. Primers are described in Table N°X. PCR fragments will be visualized in a 1% agarose gel then purified for sanger sequencing.

Table N°X Primers for *pbp-1*, *rdxA* and *frxA* gene amplification

Primer	Sequence (5'→3')	Fragment size	Ref
bp-1 Fw	CGATAGATTTGGATTACCAACGC	1035 bp	
pbp-1 R	ACGATTTCTTTACGCAAGCC		
rdxA Fw	GCAGGAGCATCAGATAGTTCT	886 bp	
rdxA R	GGGATTTTATTGTATGCTACAA		
frxA Fw	GGATATGGCAGCCGTTTATCATT	780 bp	
frxA R	GAATAGGCATCATTTAAGAGATTA		

To perform host CYP2C19 polymorphisms genotyping real time PCR using TaqMan probes for the Drug Metabolism Genotyping Assay of the to detect variants *2 (c.681G >A; rs 4244285), *3 (c. 636G >A; RS 4986893) and *17 (−806C >T; RS 12248560).

Covariates

1. Sex
2. Age
3. BMI
    a. Weight
    b. Size
4. Socioeconomic status: Income, activity, level of education.
5. Comorbidities
    a. Use of medications

6. Family history of *Helicobacter pylori*
7. Feeding Patterns
8. Degree of Therapeutic Adherence: A Spanish version of The Morisky scale of medication adherence (MMAS-8) (25), which has already been used in Chile (26), will be adapted and applied.

Questions	Answer Options	Assigned score
1. Have you forgotten to take the medicine for *Helicobacter pylori*?	Yes/No	0/1
2. Some people miss taking their medicines for other reasons and not just forgetting. If you remember the last two weeks, was there a day when you forgot to take the medicine for *Helicobacter pylori*?	Yes/No	0/1
3. Have you reduced your dose or stopped taking the medicine because you felt worse about taking it?	Yes/No	0/1
4. When traveling or away from home, do you ever forget to bring *the medicine for Helicobacter pylori* ?	Yes/No	0/1
5. Did you take the medicine for *Helicobacter pylori* yesterday?	Yes/No	0/1
6. When you feel that your stomach discomfort is under control, have you stopped taking your *Medicine for Helicobacter pylori*?	Yes/No	0/1
7. Taking medication every day can be a problem for many people. Do you ever feel pressured to follow medical treatment for *Helicobacter pylori*?	Yes/No	0/1
8. How often do you have trouble remembering to take all your medicines?	Never/Almost never Seldom Sometimes Habitually Always	1 0,75 0,5 0,25 0

Covariates will be recorded at recruitment. For ADRs and therapeutic adherence telephone follow-up will be performed on days 7 and 14 and 21 after initiation of the therapy. The last follow-up will be performed in person at the time of the UBT.

Sample size calculation

For sample size calculations the following are considered:

Table 2. Parameters for the calculation of sample size. Values obtained from a Chilean population study (23).

Variable	Value

Expected Eradication rate with control therapy scheme	82%
Expected Eradication rate with intervention therapy scheme	97%
Expected absolute difference between therapies	15%
Power	80%
Confidence	95%

This calculation shows that 65 participants per branch are needed. Calculations were performed with statistical program Stata 15 (27). Considering a loss of 10.0%, 72 patients per branch are considered. In addition, we considered 30 additional patients in case the groups resulting from randomization are not balanced and it is necessary to adjust the effectiveness of the treatments, by 3 variables to be able to make regression analysis. With this, a total of 102 patients per branch will be included in this study.

Methods used to generate the sequence for patient random assignment to branches

For the assignment of participants in the intervention or control branches, a list of random numbers will be used in the sequencing of containers containing the control or intervention treatments. They will be delivered to the study participants according to the order in which they are recruited. The process is showed in Figure 1.

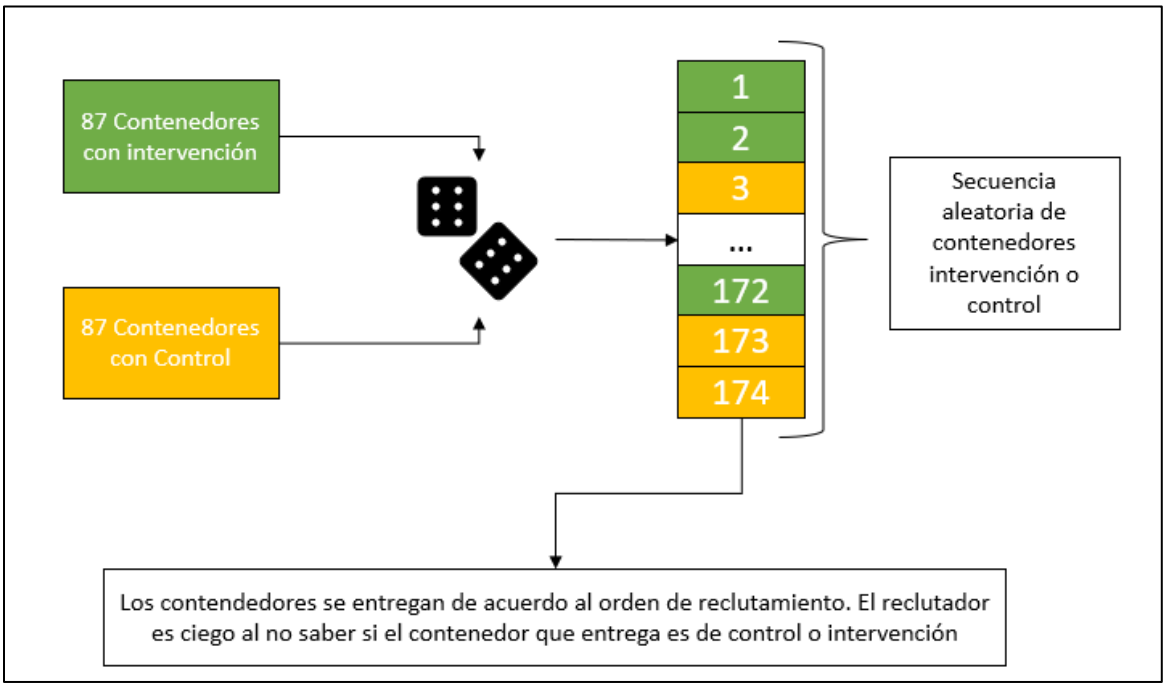
Mechanism used to implement branch random assignment

For the anonymization of the sequence, the research team will delegate the generation of the random sequence and the numbering of the containers to a team that has no participation or knowledge of the design of the study, the collection or analysis of data.

Generation of the assignment sequence, recruitment of participants and assignment of participants to the intervention's responsibilities

The research team will deliver 174 containers with the intervention or control (87 of each) to 2 members of the UC Pharmacology and Toxicology Program. They will generate the randomization sequence, number the containers according to their result and keep the record of the randomization sequence until the data collection is finished, and the statistical analysis is done then the blind opens. In this way responsibilities are assigned to:

Figure 1. Randomization system of study participants.



A. Generation of the branch assignment sequence: UC Pharmacology and Toxicology Program
B. Participant Recruitment: Principal Investigator
C. Assignment of participants to the interventions: Principal investigator delivers the containers to the participants, keeping the blind by the randomization and previous numbering of the containers.

Blind status maintenance for participants and research team

To maintain a blind status to branch assignment:

A. Part of the research team that performs patients recruitment
B. Part of the research team that performs follows up on participants
C. Part of the research team that performs test for confirmation of eradication of *H. pylori*
D. Part of the research team that performs statistical analysis

If relevant, the description of the similarity of the interventions

Each participant will receive a box that was previously randomized, the contents of the boxes are:

Container with Intervention therapy scheme	Container with Control therapy scheme

1. 42 tablets of esomeprazole 40 mg 2. 42 amoxicillin tablets of 1. 000 mg 3. 42 tablets of metronidazole 500 mg 4. 63 bismuth Subsalicylate tablets 246 mg 5. Therapy administration instructions	1. 28 omeprazole tablets 20 mg 2. 28 amoxicillin tablets of 1. 000 mg 3. 28 tablet of clarithromycin 500 mg 4. 42 bismuth Subsalicylate placebo tablets 5. Therapy administration instructions

The control and intervention containers will look the same.

Statistical methods used for group comparison of primary and secondary outcomes

General

The statistical analysis will be performed without knowledge of therapy scheme assignment, or the clinical evaluation of participants included in the study. P values <0,05 will be considered statistically significant. The analyses will be carried out under the *intention-to-treat* (ITT) modality.

Registration and safeguarding of the data collected

Data logging has 3 stages:

1. Recruitment
2. Telephone follow-ups days 7, 14 and 21 after starting treatment.
3. UBT exam between 8 and 12 weeks after treatment ends.

Each of these stages will have a physical record on paper, which will be transcribed into the REDCap electronic registry. The paper records will be maintained under lock and key at the Toxicological and Drug Information Center (CITUC), located at Lira 63, second floor.

Regarding the quality of the data recorded

At the time of analysis, a random sample of 10% of the participants will be selected to evaluate the consistency between the physical and electronic record. If there are doubts in the quality of the information, all records will be checked. Anomalous values will also be checked in the physical register.

Data Analysis Plan

Descriptive Statistics

Descriptive statistics will be performed to determine the characteristics of the complete cohort and stratified by experimental branch. The balance of the intervention and control groups will be evaluated. If the balance is not reached, the effect will be directly adjusted with multivariate models.

Primary analysis: Comparison of treatment efficacy

We will perform comparison for eradication percentages between groups by inferential statistical tests, to determine whether the difference between the groups reaches statistical significance. We will also calculate Relative risk measures. We will analyze variables associated with positive eradication and perform a multivariate analysis of factors associated with eradication using binomial regression.

Secondary analysis: Adverse drug reactions

Adverse reactions

We will perform descriptive statistics, by type, particular symptom, and temporal evolution. Comparison between control and intervention branches will be analyzed by the magnitude of ADR observed. Evaluation of association between ADR s with treatment scheme and covariates, by regression will be performed

Sensitivity analysis

To evaluate the robustness of the results, the analysis will be repeated in the modality by protocol to compare them with those obtained under the intention-to-treat modality. Secondly, the effect of therapeutic adherence will be evaluated. The analysis will also be stratified by the measured covariates, to evaluate sources of uncertainty, confusion, or possible interactions.

Ethical Aspects

Admission to the study is conditional on the reading and signing of informed consent, after the potential participant has understood what their participation consists of, as well as the risks and benefits associated with it. This study will be implemented and conducted in accordance with the Declaration of Helsinki and Ethical clinical practices.

All drugs that will be used to conduct this research, both in the intervention and control branch are approved by the Institute of Public Health of Chile. They will be used within the typical therapeutic ranges of use thus interventions are considered safe for the study participants. Endoscopies, venous sampling and UBT are all performed in centers of the UC-CHRISTUS Health Network, under standardized protocols that ensure the quality and safety of the procedures.

Participants who fail to eradicate *H. pylori* will be treated using under standard of care conditions by the gastroenterology team that is part of the research team, at no cost.

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