UNIVERSIDAD NACIONAL DE COLOMBIA
SEDE BOGOTÁ

IMPACT OF HEAD OF BED ELEVATION IN SYMPTOMS OF PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE: A RANDOMIZED SINGLE-BLIND STUDY (IBELGA)

INTERNAL MEDICINE POSTGRADUATE THESIS PROTOCOL

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EXECUTIVE SUMMARY

Background: Gastroesophageal reflux disease is a very frequent clinical condition and nocturnal symptoms are a cause of quality of life impairment, poor sleep quality and absenteeism. Because of factors such as a prolonged acid exposure during sleep, nocturnal reflux has been associated to esophagitis, more extra-esophageal symptoms and other illnesses such as asthma. Head of bed elevation, as a low-cost non pharmacologic anti-reflux treatment is nowadays recommended, but its clinical impact in patients with nocturnal symptoms remains unknown due to inconsistent results and methodological limitations among different clinical trials, most of which were performed before the widespread use of proton pump inhibitors in clinical practice.

Hypothesis: Head of bed elevation is a useful treatment for patients with gastroesophageal reflux disease and nocturnal symptoms, and has a positive impact in quality of life in these patients.

Study Objective: To assess the effectiveness of head of bed elevation for treatment of patients with gastroesophageal reflux disease and nocturnal symptoms, and to determine the impact of this intervention in quality of life of these patients.

Methods: Randomized single-blind single-centre controlled clinical trial with a 2x2 cross-over design. A sample of 42 patients attending to the outpatient gastroenterology unit at Clínica Fundadores in Bogotá city, who meet the inclusion criteria and have no exclusion criteria will be selected to participate. Included patients will be randomized to raise the head of bed with standard 20 cm-height wooden blocks or to sleep without bed inclination during the first 6 week period. After a 2 week washout period, allocation will be crossed and participants will be followed again during a second 6 week period. During the trial, every patient will receive standard pharmacological treatment with a proton pump inhibitor and/or sodium alginate and the researchers in charge of statistical analysis and reporting results will be blinded for the non pharmacological intervention under study. Primary outcome is a significant symptom reduction according to RDQ validated questionnaire and secondary outcomes include quality of life impact according to SF-36 validated questionnaire, patient preference and adverse events of non pharmacological intervention. Statistical analysis will be carried out with STATA 13.0 (Special Edition) statistical package for Windows. Differences with a $p<0,05$ will be accepted as statistically significant.

Expected results: Effectiveness of head of bed elevation in the treatment of patients with symptomatic nocturnal gastroesophageal reflux disease will be assessed. New knowledge for generation of a local and international recommendation about non pharmacological treatment of gastroesophageal reflux disease will be provided. Colombian researchers will be trained in methodological aspects concerning design, conduction and analysis of clinical trials in this field of medical knowledge.

Keywords: Gastroesophageal reflux disease, head of bed elevation, lifestyle measures, nocturnal symptoms, quality of life.

PROBLEM STATEMENT

Gastroesophageal reflux disease (GERD) is a clinical condition characterized by troublesome symptoms and medical complications as a result of reflux of gastric contents into the esophagus[1]. GERD is diagnosed in 4% of primary care outpatient visits[2] and the disease prevalence in Latin-America reaches 12-31%[3]. Nocturnal symptoms have been found in 74% of patients with GERD and are a cause of significant quality of life impairment, when compared with general population and

patients with GERD and daytime-only symptoms[4]. Sleep interference secondary to nocturnal retrosternal burning has been associated to lower work productivity[5], even in patients being treated with proton pump inhibitors (PPI)[6]. Due to several physiological factors such as lack of conscious perception of symptoms, reduced salivation and a lower frequency of nocturnal swallowing[7], a significantly longer acid exposure overnight has been associated to the emergence of complications like esophagitis[8, 9], more extra-esophageal symptoms[10] and other illnesses such as asthma[11].

As a low-cost non pharmacological anti-reflux treatment for GERD, head of bed elevation (HBE) is nowadays moderate-strength recommendation with a low level of evidence[12-15]. Clinical impact of this measure in patients with night-time symptoms remains unknown, due to inconsistent results and methodological limitations among different clinical trials; most of which were performed before the widespread use of proton pump inhibitors in clinical practice. Evidence from several non-randomized studies suggest that HBE could reduce esophageal acid exposure time and could decrease GERD symptoms[16-18]; however, another study found no significant differences in those same outcomes[19]. On the other hand, all randomized controlled clinical trials published this far show inconsistent results. A study published before widely accepted clinical use of PPI, revealed significant clinical and endoscopic improvement in patients with GERD and grade C-D esophagitis allocated to receive HBE, when compared with controls[20]. In contrast, a multi-centre clinical trial found no difference in symptom score or antacid use among groups allocated to HBE and control group[21]. All cited studies have methodological limitations and heterogeneity in outcome assessments, which makes difficult conducting a meta-analysis with these data[22, 23]. No published studies evaluating impact of HBE in quality of life or work productivity were found. Table 1 summarizes published evidence to date.

Study [Population]	Jadad score	Follow-up	n	Major findings	Main limitation	Reference
Stanciu C, 1977 [GERD]	**1**	**15 hours**	**63**	**↓ acid exposure time, clinical improvement**	**Non-randomized Short follow-up**	**16**
Johnson L, 1981 [GERD]	**0**	**ND**	**55**	**↓ acid exposure time**	**Non-randomized No symptom assessment**	**17**
Harvey R, 1987 [C/D Esophagitis]	**3**	**6 weeks**	**71**	**Clinical and endoscopic improvement**	**Pre-PPI era**	**20**
Hamilton J, 1988 [Esophagitis]	**3**	**3 days**	**15**	**No acid exposure time reduction nor clinical improvement**	**Low power Short follow-up**	**19**
Pollmann H, 1996 [GERD]	**NA**	**2 weeks**	**NA**	**No clinical improvement**	**Full text unavailable Non-structured abstract**	**21**
Khan BA, 2012 [Nocturnal GERD]	**1**	**1 week**	**20**	**↓ acid exposure time, clinical improvement**	**Non-randomized Inpatient setting**	**18**

Table 1: Summary of HBE clinical trials in GERD published to date. NA: Unavailable; PPI: proton pump inhibitor; ↓: reduction

HYPOTHESIS

Head of bed elevation is a useful treatment for patients with GERD and nocturnal symptoms, and has a positive impact in quality of life in these patients.

STUDY OBJECTIVES

General Objective: To assess the effectiveness of HBE for treatment of patients with GERD and nocturnal symptoms, and to determine the impact of this intervention in quality of life of these patients.

Specific Objectives:

1. To identify, recruit and randomize participants with strict allocation concealment.
2. To compare symptom severity and quality of life among participants allocated to the HBE and the control group, in both the first and second period of study.
3. To assess therapeutic adherence and adverse event occurrence periodically by means of telephone call and photographic documentation of patient compliance with assigned intervention.

PATIENTS AND METHODS

General design: Randomized single-blind single-centre controlled clinical trial with a 2x2 cross-over design, in a sample of patients attending to the outpatient visit at the Gastroenterology, Digestive endoscopy and Liver Diseases Unit in Clínica Fundadores, Bogotá city. Participants who meet the inclusion and have no exclusion criteria will be randomized to raise the head of bed with standard 20 cm-height wooden blocks or to sleep without bed inclination during 2 periods of 6 weeks each, separated by a washout 2 week period. During the trial, every patient will receive standard pharmacological treatment with a proton pump inhibitor and/or sodium alginate, according to treating physician criteria, and the researchers in charge of statistical analysis and reporting results will be blinded for the non pharmacological intervention under study. Primary outcome is a significant symptom reduction according to RDQ validated questionnaire and secondary outcomes include quality of life impact according to SF-36 validated questionnaire, patient preference and adverse events of non pharmacological intervention.

The trial will be conducted during 8 months and will be divided into 4 successive stages.

1. **Stage I:** 2 months during which the first 4 specific objectives will be accomplished.
2. **Stage II:** 4 months for specific objectives 5 to 7.
3. **Stage III:** 1 month for specific objective 8 and results discussion.
4. **Stage IV:** 1 month for specific objectives 9 and 10.

In figure 1 and table 2, different stages with respective component activities are outlined.

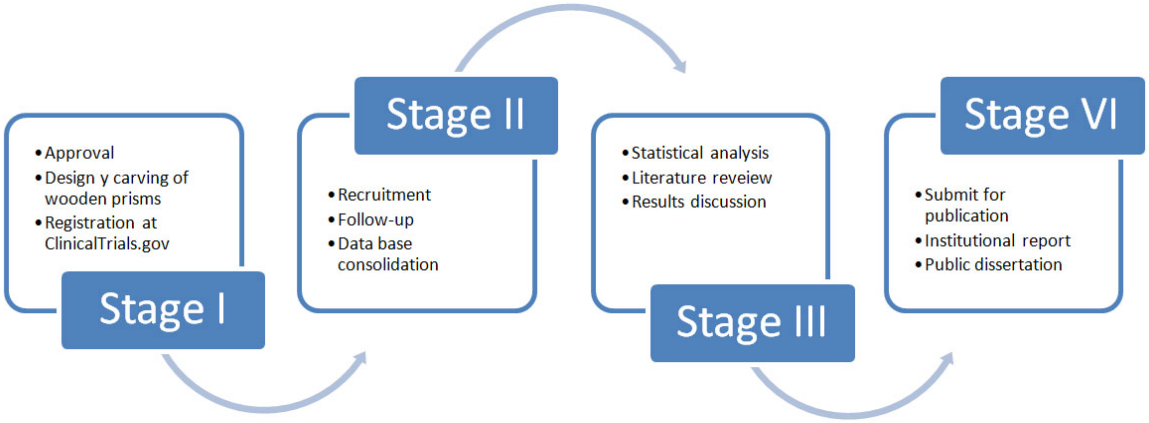

Figure 1: Clinical trial stages

Patient recruitment: Because of a low recruitment rate, an active participant search system was finally implemented. This system was based on telephone calls, using a database with patient data from all upper gastrointestinal endoscopies performed in the Gastroenterology Unit at Clínica Fundadores in Bogotá city, between years 2014 to 2016. Patients were pre-selected based on endoscopically diagnosed erosive esophagitis of any grade, which is one of the clinical trial inclusion criteria. In order to minimize selection bias, 2 interviewers performed telephone calls in a consecutive chronologic order to all patients in the database without exception. In all cases, the same standardized telephone call format was used.

Sample size: Null hypothesis (H_0) and unidirectional alternative hypothesis (H_1) of the trial are represented below:

$$H_0: RDQ_{HBE} = RDQ_{NoHBE} \qquad H_1: RDQ_{HBE} < RDQ_{NoHBE}$$

$$H_0: SF\text{-}36_{HBE} = SF\text{-}36_{NoHBE} \qquad H_1: SF\text{-}36_{HBE} > SF\text{-}36_{NoHBE}$$

Sample size was estimated based on the hypothesis that HBE would produce a difference of at least 10% in RDQ and SF-36 scores. Effect size (Cohen d) was calculated as 0,49 keeping in mind an RDQ mean and standard deviation of 3,3±1,0 previously found in Spanish population with symptomatic GERD[24] and an SF-36 mean and standard deviation of 56,9±20,3 reported in Italian population in medical therapy with PPI[25]. The minimally important difference selection was chosen based on the assumption that any difference smaller than 10% would have no clinical relevance. Based on this data, 14 patients per group would yield a power greater than 80% for detection of a minimally important difference as large as or larger than 0,6 points in RDQ questionnaire (range: 1 to 6) and 10 points in SF-36 questionnaire (range: 0 to 100), when using a paired t test as described in the statistical analyses plan section. Because of a complementary analysis of crossover data is planned with McNemar marginal homogeneity test, effect size was recalculated based on results of a previous trial[20], according to which, 58,8 % and 28,6% of placebo-treated patients in pre-omeprazole era, reported improvement of GERD symptoms with and without a HBE of 20 cm, respectively. Based on these data, and maintaining a statistical power of 80%, required sample size was adjusted to a total of 34 patients. In

figure 2, matrices for sample size calculation are shown, based on the cited trial and using internationally accepted statistical procedures[26]. Likewise, in table 3 an output of sample size calculation is shown from G*Power 3.1.9.2 (Universität Düsseldorf, Düseldorf, Germany) software[27]. Finally, calculated sample size was increased by 20% in order to avoid study power loss due to drop-outs or losses of follow-up. Thus, final sample size was 42 patients, 21 per group.

T test	Means: Difference between two dependent means (matched pairs)	
Analysis	A priori: Compute required sample size	
Input	Tails	One
	Effect size dz	0,4926108
	A err prob	0,05
	Power (1- β err prob)	0,8
Output	Noncentrality parameter δ	2,5596808
	Critical t	1,7056179
	Degrees of freedom	26
	Total sample size	27
	Actual power	0,8015888
McNemar	Proportions: Inequality, two dependent groups	
Analysis	A priori: Compute required sample size	
Input	Tails	One
	Odds ratio	3,571
	α	0,05
	1- β	0,8
	Prop discordant pairs	0,53782
Output	Lower critical N	13,0000000
	Upper critical N	13,0000000
	Total sample size	34
	Actual power	0,8169370
	Actual α	0,0481262
	Proportion p12	0,4201608
	Proportion p21	0,1176592

Table 3: Sample size calculation output with G*Power 3.1.9.2 software[27]

Inclusion criteria:

Patients with GERD who meet with all the following characteristics:

1. Diagnosis of GERD based on Montreal definition (Esophageal erosions and typical symptoms such as pyrosis and/or regurgitation with a frequency ≥ 2 times per week).
2. Retrosternal pyrosis lasting ≥ 3 months.
3. Pyrosis and/or regurgitation with a frequency ≥ 3 nights per week
4. GERD-associated sleep disturbance (insomnia, poor sleep quality) with a frequency ≥ 3 nights per week, and lasting ≥ 1 month.

Exclusion criteria: Patients with atypical symptoms and no erosions on endoscopy (NERD: Non-erosive Gastroesophageal Reflux Disease) will not be included. Likewise, patients with the following situations will be excluded from the trial: peptic ulcer, history of biliary surgery, lactating or pregnant women, participants under 18 years of age and nighttime shift workers (12 am to 6 am). Patients with the following conditions which affect sleep quality will also be excluded: Obstructive sleep apnea

hypopnea syndrome, chronic obstructive pulmonary disease, patients with nocturnal supplementary oxygen requirement, orthopnea, nocturia, restless legs syndrome, patients consuming more than 3 cups of coffee per day, patients planning to travel beyond 3 time zones during study, patients being treated with sleep medication (e.g. anxiolytics, antihistamines, benzodiazepines) for less than 3 months or when suspension or dose modification of this drugs is being planned during the study course.

Design and carving of wooden prisms: 124 prisms of withered pine tree wood with dimensions 20x18x18 cm will be carved from 9 logs of 300x20x20 cm at Aserrío San Ignacio Ltda. production plant, located in Soacha, Cundinamarca. Given it is an industrial process of chainsaw cutting and wood planning, a quality control will be implemented consisting of verification of prism stability while lying on the floor, and the mean height in millimeters of every prism will also be measured and registered. Unsteady products or those with atypical mean heights, defined as a height either exceeding percentile 75 + 1,5 times interquartile range or below percentile 25 – 1,5 times interquartile range, will be discarded and not used during the study. As shown in figure 3, this non-pharmacological intervention was designed to obtain an inclination range dependent on the bed length of each patient (usually 1,90 cm in local industry). After exclusion of defective prisms, n groups of wooden prism pairs according to mean height in millimeters will be formed and every group will be given a random digit generated by computer. Afterwards, every random digit of prism groups will be sequentially assigned to a consecutive HBE-allocated patient number, in such a way that every consecutive patient number (among those allocated to HBE) will be linked randomly to a preset known prism height. This additional randomization procedure, involving prisms according to their mean height, is planned due to the impossibility to guarantee that prism height will be identical with a precision of ±1 mm, keeping in mind that products will be cut with chainsaw and will be planed as part of an industrial process.

	Improved with treatment B		
Improved with treatment A	**No**	**Yes**	**Total**
No	r	s	r+s
Yes	t	u	t+u
Total	r+t	s+t	N pairs

$$\textbf{Discordant pairs} = \frac{s+t}{\textbf{N pairs}} = 53,8\% \quad \textbf{OR} = {}^{s}/_{t} = 3,57$$

	Improved without HBE		
Improved with HBE	**No**	**Yes**	**Total**
No	29,4%	11,8%	41,2%
Yes	42%	16,8%	58,8%
Total	71,4%	28,6%	100%

Figure 2: Matrices for sample size calculation, according to reference 20 and 26. HBE: Head of Bed Elevation.

In figure 4, a quality control graph is shown. Mean wooden prism height was a non-normal variable when Shapiro-Wilk test was applied (W: 0,908; critical W: 0,979; p: 0.000000). After using predefined exclusion rules for atypical values, 2 pairs of wooden prisms were discarded.

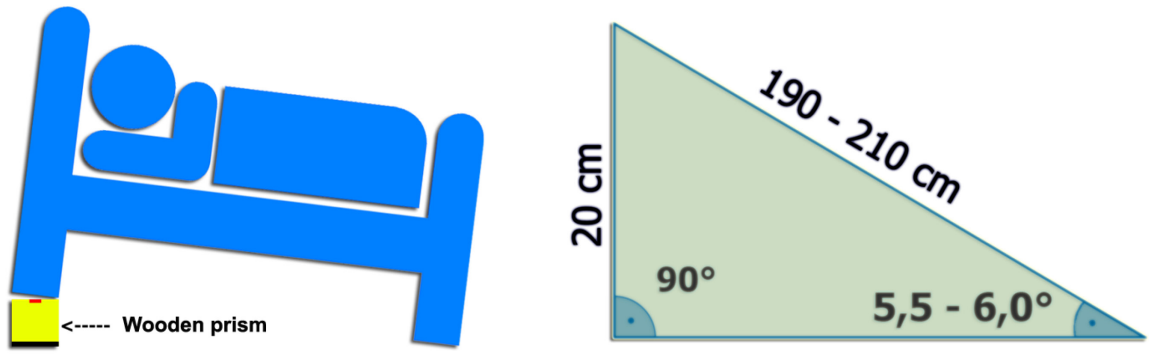

Figure 3: Schematic representation of HBE and expected bed inclinations.

Randomization: A list of 42 numbers will be generated, with subsequent binomial transformation, by using STATA 13.0 software for Windows (StataCorp LP, Texas, USA) in order to allocate participants in a 1:1 proportion to each one of the study arms. Wooden prisms will be marked with a consecutive number from 1 to 42 and they will be stored, keeping the marked number out of reach from the sight of the researcher in charge of patient recruiting.

Patients that meet the inclusion criteria, have no exclusion criteria and who give written informed consent, will be assigned a consecutive number during their outpatient visit according to their order of inclusion in the trial. These participants will be randomized to either HBE or control group in the moment that a member of the research team verifies, among the stored prisms, the existence of a prism pair marked with the same number as the consecutive number assigned to the patient. In the case that this pair does exist, then the patient will take home that pair of wooden prisms and use them during the first period of the trial according to spoken and written instructions to be given at that moment. On the contrary, if a pair of wooden prisms marked with the same consecutive number as the patient, does not exist, then it will be understood that the study participant has been allocated to control group during the first period of the trial. The member of the research team who verifies the storehouse of wooden prisms will not be in charge of confirming inclusion and exclusion criteria and will not assign consecutive numbers to patients during outpatient visits.

Allocation concealment: The researcher in charge of confirming inclusion and exclusion criteria, fulfilling the Basic Data Formulary and providing the patient with the Informed Consent Format, will not be aware of the allocation sequence order until these 3 documents have been applied to the participant and a consecutive number has been generated according to their order of inclusion in the trial. After that, a member of the research team in the prism storehouse will verify the existence of a prism pair marked with the same number as the consecutive number assigned to the patient, and only in that point allocation status of the participant will be known.

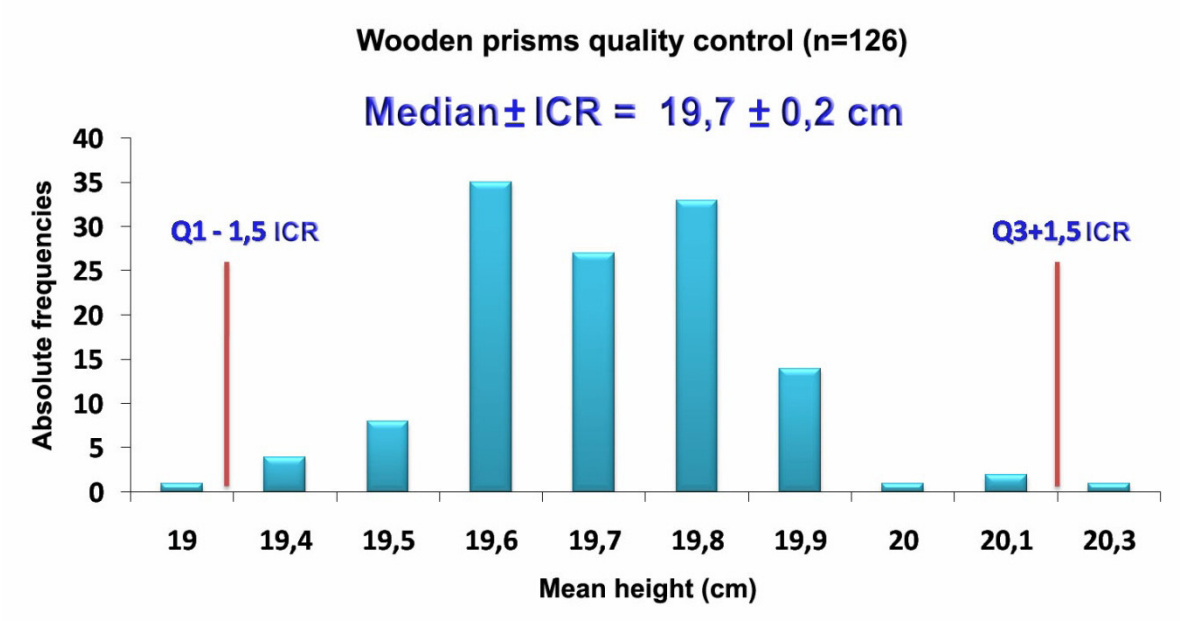

Figure 4: Wooden prisms quality control. ICR: Interquartile range; Q1: Quartile 1; Q3: Quartile 3.

Cross-over: After allocation has been completed, patients in the intervention group will receive a pair of numbered wooden prisms with dimensions 20x18x18 cm along with written instructions about the correct use of the intervention. The patient must sleep with HBE during 6 weeks and both RDQ and SF-36 questionnaires will be applied again at the end of this first period while the participant is still sleeping with HBE. Afterwards, a washout 2 week period follows in which the participant sleeping with HBE will stop using it and will return the pair of wooden prisms to the researchers. After washout period has ended and both RDQ and SF-36 questionnaires have been applied again, patients allocated to the control group during the first period of the study will receive a random pair of prisms and will be instructed to use the prisms for sleeping with HBE during a second period of 6 weeks. Meanwhile, participants initially allocated to the HBE group will be followed as a control group in this second period of the study.

Blinding: Because HBE is not susceptible to double-blinding, patients allocated to the intervention group will always be aware of the group they belong to. However, the researcher in charge of statistical analysis of data and writing the results report will work with random-generated alphabetical group codes for masking the intervention in each one of the periods of the trial.

Follow-up: After participant allocation, telephonic follow up will be made during both periods of the trial with a frequency that is dependent on the intervention group of the patient in that period. Participants in the HBE group will be called weekly for 2 weeks, and then will be called biweekly for a month, until each period of 6 weeks has ended. In contrast, patients in the control group will be called every three weeks along each period. With the purpose of verifying both HBE adherence and correct use of wooden prisms, every participant will be asked to send a photograph of the bed head legs during the follow-up telephone call. The photograph will be received by the researcher via e-mail or smart-phone and will be encoded and saved in a hard disk. At the end of the first period, RDQ and SF-36 questionnaires will be applied and researchers will store the returned prisms during washout period. When washout period has ended, RDQ and SF-36 questionnaires will be applied again in order to be sure of the absence of any *carry-over* effect in the group initially allocated to HBE. Finally at week 14, RDQ, SF-36 and Patient Preference questionnaires will be administered to complete study ending outcome assessments.

In figure 5, a schematic representation of follow-up is shown.

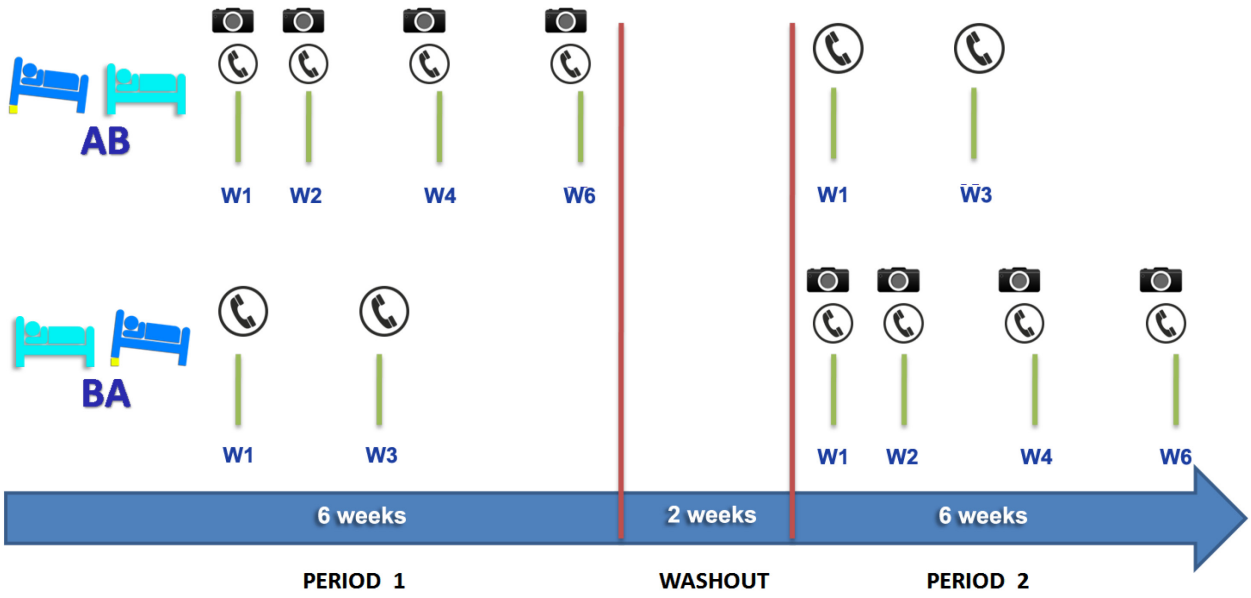

Figure 5: Schematic representation of photographic and telephonic follow-up. W1-6: Weeks from 1st to 6th in each period.

Primary outcome:

1. **Effectiveness:** Change of ≥ 0,6 points between basal RDQ questionnaire and the same questionnaire administered after 6 weeks of HBE use.

Secondary outcomes:

1. **Quality of life:** Change of ≥ 10 percentage points between basal SF-36 questionnaire and the same questionnaire administered after 6 weeks of HBE use.

2. **Patient preference:** Proportion of patients who preferred HBE, after finishing 14 weeks of the study.

3. **Safety:** Proportion of patients with any reported adverse event during HBE or without bed inclination.

Statistic analysis plan: Quantitative and qualitative variables collected with Basic Data Format, RDQ, SF-36 and Patient Preference questionnaires will be typed in a Microsoft Excel 2007 database. Intervention groups will be masked with an alphabetical code provided by an independent collaborator who will not be involved with data analysis or report writing. For statistical processing, database will be imported into STATA SE 13.0 for Windows (StataCorp LP, Texas, USA) and descriptive statistics will be generated for each variable. Statistically significant differences will be searched for categorical data using the Chi-square test or Fisher exact test and normality will be tested for numerical continuous variables using the Shapiro-Wilk test. For normally distributed continuous variables, statistically significant differences will be searched for by using unpaired Student's t test. Alternatively, for not normally distributed variables Mann-Whitney U test will be applied. For non-normal variables due to atypical data, values outside the percentile 50 ± 1,5 interquartile range were excluded. For complementary processing of primary outcome and secondary outcome quality of life, score difference

between periods will be transformed into a binomial variable and a McNemar marginal homogeneity test will be applied. McNemar mid-p was used if discordant pairs sum was smaller than 25[28]. Differences with one-tail p<0,05 will be accepted as statistically significant. Exploratory subgroup analysis will search for differences stratified according to age group, sex, ethnic group, BMI, comorbidities, cups of coffee per day, pharmacological adherence, and length and severity of symptoms; among other 16 baseline variables. Subgroup interactions will be tested with Chi-square or Fisher exact test, and effect size was expressed as a univariate relative risk from a generalized linear model of binomial family. As part of internal quality control of the clinical trial, a pre-test was applied to prove the assumption of a negligible *carry-over* effect, according to expert guidelines[29]. Analysis of variance (ANOVA) for crossover studies was used in search for significant sequence, period and treatment effects, assuming a negligible *carry-over* effect. In the modified intention to treat analysis, participants with protocol violations because of bad adherence to HBE, were included, but it was not possible to include patients who withdrew from the study because outcome information could not be gathered completely.

Methodology diagram: A schematic representation of the trial methodology is presented in figure 6.

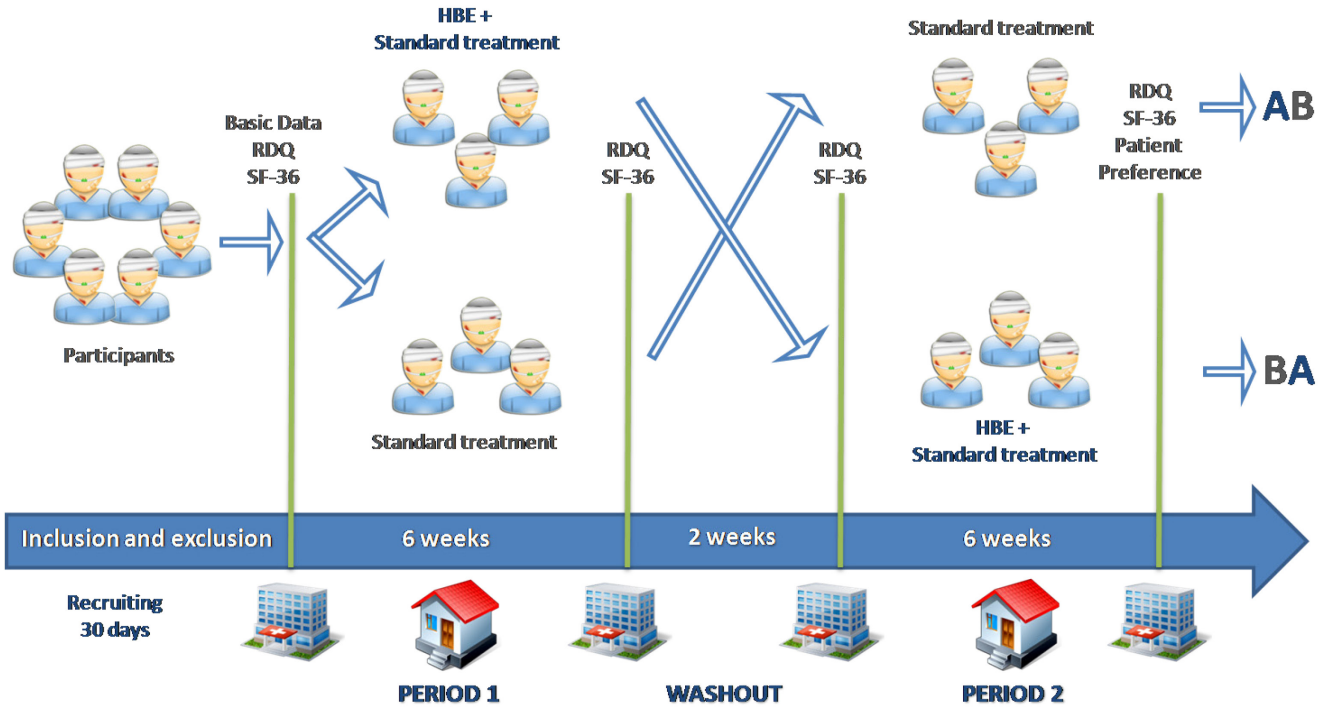

Figure 6: Schematic representation of the trial methodology. RDQ: Reflux Disease Questionnaire; SF-36: Short Form 36 Questionnaire; HBE: Head of Bed Elevation; Standard treatment: Based on proton pump inhibitors and/or sodium alginate, according to treating physician criteria.

WORK TEAM

Work team of this clinical trial is formed by three authors. The respective roles during the design and conduction of the trial, and also the professional profiles of each researcher are described below.

Researchers:

- **Iván Mauricio Villamil Morales** (Principal Researcher – study design, patient recruiting, telephonic follow-up, outcome assessment, statistical analysis, writing of final report)
  - General Practice Physician – Universidad Nacional de Colombia
  - 3rd year Internal Medicine resident – Universidad Nacional de Colombia

- **Daniel Mauricio Gallego Ospina**(Researcher – patient recruiting, intervention administration, clinical and telephonic follow-up, writing of final report)
  - General Practice Physician – Universidad Nacional de Colombia
  - 3rd year Internal Medicine resident – Universidad Nacional de Colombia

- **William Otero Regino** (Researcher and project mentor – study design, critical appraisal of study results, writing and correction of final report)
  - General Practice Physician – Universidad Nacional de Colombia
  - Internal Medicine Specialist – Universidad Nacional de Colombia
  - Master of Science in Epidemiology – Universidad del Rosario
  - Gastroenterologist – Universidad Nacional de Colombia
  - Gastroenterology in Chief – Clínica Fundadores - Bogotá

Researcher's curriculum vitae (CvLac) can be consulted on-line in the Sistema Nacional de Ciencia y Tecnología (Colciencias) platform.

ETHICAL AND LEGAL ISSUES

Regardless of being a randomized controlled clinical trial, the intervention to allocate in the present study is not a drug but a non-pharmacological intervention (HBE). Therefore, ethical considerations were not based on Resolution 2378 of 2008.

According to express classification from article 11 from Ministerio de Salud Resolution 8430 of 1993, the present study has minimal risk for participants[30]. No severe or persistent adverse events of HBE have been reported in clinical trials published this far[16-20]. Only one of the cited trials reported 2 adverse events, namely: recurrent slipping out of bed without falling and slight sexual problems associated with bed position, although they were resolved quickly[20]. Based on low frequency of these adverse events, mildness and rapid resolution, it was not deemed necessary to buy a collective insurance policy to cover eventual compensations. Likewise, impartial allocation of participants will be achieved by randomization and their safety will be supervised during follow-up. Neither researchers nor patients will be exposed to major risks during the trial.

Alfa-numeric encoding will be implemented in order to protect identity of the participants and management of data will be confidential. Any essential change in study protocol, trial conduction or any future use of study data will be consulted with Medicine Faculty Ethics Committee at Universidad Nacional de Colombia.

Informed Consent will be provided for all study participants and it will be signed in case of patient agreement. The Informed Consent Format was made according to articles 15 and 16 from Ministerio de Salud Resolution 8430 of 1993 (**Appendix A**).

Researchers declare no conflicts of interest. If such conflicts emerged during study conduction, they will be presented to the Medicine Faculty Ethics Committee at Universidad Nacional de Colombia. Likewise, this clinical trial is in accordance with article 13 from Ministerio de Salud Resolution 8430 of 1993, which highlights research institution responsibility of providing medical care to participants who suffer damage directly related to being part of a clinical trial.

TIMELINE OF ACTIVITIES

STAGE/ACTIVITY	Stage I (2 months)		Stage II (4 months)						Stage III (1 month)		Stage IV (1 month)	
Administrative												
Protocol writing	X											
Faculty Ethics Committee	X	X										
Wooden prism carving		X										
Data collection												
Patient sampling			X	X								
Basal questionnaires			X	X	X	X	X	X				
Post-intervention questionnaires					X	X	X	X	X	X		
Database consolidation			X	X	X	X	X	X	X	X		
Data analysis												
Statistical analysis									X	X		
Literature review									X	X		
Results discussion										X		
Results disclosure												
Preliminary report									X		X	
Final report												X
Public dissertation												X
Original paper writing											X	X
Submit to publication												X

Table 2: Research Project proposed timeline

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APPENDIX A

UNIVERSIDAD NACIONAL DE COLOMBIA
SEDE BOGOTÁ
FACULTAD DE MEDICINA

INFORMED CONSENT FORMAT

STUDY INFORMATION

- ✓ Research project objective: To assess the effectiveness of head of bed elevation for treatment of patients with gastroesophageal reflux disease and nocturnal symptoms, and to determine the impact of this intervention in quality of life of these patients.
- ✓ Research project justification: Head of bed elevation, as a non-pharmacological anti-reflux low-cost intervention, is actually recommended, but its clinical impact on patients with nocturnal reflux remains unclear, due to lack of consistency and methodological interventions in different previous studies.
- ✓ Procedure to follow:
  - Fill in provided questionnaires at the beginning, midpoint and ending of clinical trial.
  - Sleep during 6 weeks with head of bed elevation, using standard wooden blocks of 20 cm in height.
- ✓ Expected nuisances or risks: None.
- ✓ Possible benefits: Useful knowledge will be provided to generate a local statement about non-pharmacological treatment of gastroesophageal reflux disease, and a contribution will be produced with intention to modify international guidelines recommendation about this subject.

INFORMED CONSENT

I declare that my name is _____, owner of identification card number _____ emitted in _____. I accept to participate in the clinical trial called "Impact Of Head Of Bed Elevation In Symptoms Of Patients With Gastroesophageal Reflux Disease: A Randomized Single-Blind Study (IBELGA)" and I certify the following assumptions.

1. I have read and understood STUDY INFORMATION section and it was offered to me the opportunity to clarify any doubt concerning procedures, risks, benefits and other aspects related to this clinical trial.
2. I am free to withdrew my informed consent to participate in the trial at any moment, and I am free to quit my participation without any adverse repercussion to my healthcare and treatment.
3. Researchers have given me guarantee of respect to my right to privacy, by maintaining my clinical record data confidentiality.
4. Researchers have compromised to inform to me updated trial information during the study course, despite this information could affect my decision to carry on my participation in the trial.
5. Researchers have given me guarantee of respect to my right to medical treatment in case of any direct harm caused by my participation in this clinical trial.
6. Researchers have given me guarantee that any additional cost derived of my participation in this clinical trial will be paid with the research budget or will be charged to the institution responsible of the research project.

Signatures:

_____	_____	_____
Study participant	Witness 1 Name: Address:	Witness 2 Name: Address:

Maeya S.

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