DOCUMENT DATE: November 29, 2023

UPLOADED: 02/01/24

PROYECT TITLE: EFFECTIVENESS OF COMBINED TREATMENT FOR SMOKING CESSATION IN SUBJECTS HOSPITALIZED FOR LUNG DISEASE AND TOMOKING: AN OPEN RANDOMIZED CLINICAL TRIAL

RESPONSIBLE INVESTIGATOR AND ASSIGNMENT

Dr. Ireri Isadora Thirión Romero
Smoking and COPD Research Department.

PARTICIPANT RESEARCHERS AND ASSIGNMENTS

Dr. Víctor Adrián Flores Aceves, National Institute of Respiratory Diseases.
Dr. Arantxa Mariana Remigio Luna, National Institute of Respiratory Diseases.
Dr. Ivan Centeno Saenz, Department of Smoking and COPD Research.
Dr. José Rogelio Pérez Padilla, Department of Research in Smoking and COPD.
Dr. Sebastián Rodríguez Llamazares, National Institute of Respiratory Diseases.
Dr. Robinson Emmanuel Robles Hernández, Department of Research in Smoking and COPD.
Dr. in Psych. Ma. Andrea Hernández Pérez, Department of Research in Smoking and COPD.
Dr. in Psych. Leonor García Gómez, Department of Research on Smoking and COPD.
Dr. in Psych. Ma. Jennifer Osio Echanove, Department of Research in Smoking and COPD.

INTRODUCTION

Smoking is an addictive disease that causes a chemical toxicosis caused by the inhalation of tobacco smoke, capable of causing acute or chronic harmful effects on different structures of the body. Various factors affect the damage this activity can generate in each individual, including clinical, biological, psychological, epidemiological, and socioeconomic.(7) Tobacco smoke increases the risk of health problems that lead to hospitalization, including Cardiovascular and respiratory diseases, increases the days of hospital stay, worsens postsurgical recovery, and increases the risks of cancer.(7)

In Mexico, 14,820,107 people over 20 years of age currently smoke (18%); Of them, 4,167,375 are women, and 10,652,720 are men.(8) 51.6 thousand deaths occur annually attributable to tobacco consumption, which represents 7.5% of deaths in Mexico.(7)

The combination of psychological and pharmacological treatment for smoking cessation has been found to be more effective than separate treatments (9). Currently, the FDA has approved different medications as the first line of treatment: nicotine replacement treatments -NRT- (patches, gum, lozenges, nasal spray, and oral inhaler); and non-nicotinic treatment (bupropion and varenicline). (6)(9)

Nicotine Replacement Therapy (NRT) helps combat nicotine withdrawal symptoms by providing users with nicotine in long-acting (patch) or short-acting (mask gum, lozenges, inhaler, nasal spray) form. Use of NRT in any form increases smoking abstinence by 60% compared to placebo (RR 1.60, 95% CI 1.53–1.68). To increase effectiveness, the nicotine patch can be combined with short-acting NRT, which is more effective than using a form of NRT (RR 1.34, 95% CI 1.18–1.51) (10). Bupropion increases norepinephrine and dopamine levels and is approved as an antidepressant for smoking cessation. Increases smoking cessation rates compared to placebo (OR 1·75, 95% CI 1·52 to 2·01) (8.9). Varenicline is a partial nicotinic receptor agonist that doubles smoking abstinence rates compared to placebo (RR 2.24, 95% CI 2.06–2.43). (10) These results have been obtained in smokers treated on an outpatient basis. Rhe study of the effectiveness of these different treatments in hospitalized subjects has been little and marginally analyzed.(6) Among the studies carried out, it shows that hospitalized subjects who received treatment for smoking cessation and support had abstinence rates greater than 6 months. The analysis carried out in this study does not differentiate by type of pharmacological treatment. The predominant pharmacological treatment was NRT. (11) Smoking cessation in hospitalized patients has been associated with lower rates of postsurgical complications, better tissue healing and proliferation, and reversibility of the attenuation of inflammation mechanisms. (12,13)

Hospitalization is a vital scenario to address tobacco consumption for various reasons and benefits; among the most important are the prohibition of smoking on the hospital premises and the special availability for quitting that the smoker has during admission to a hospital admission promotes subsequent tobacco cessation because a severe illness, primarily if related to tobacco, can increase smokers' motivation to quit.

MAIN OBJECTIVE

Our objective will be to analyze the effectiveness of the combination of bupropion and nicotine versus nicotine replacement therapy to quit smoking in hospitalized subjects 12 months after discharge.

SPECIFIC OBJECTIVES

1. Analyze the effectiveness of the combination of pharmacological therapies to quit smoking in hospitalized subjects 3, 6 and 12 months after discharge.

2. Evaluate the symptoms and signs of withdrawal in the different groups throughout their follow-up.

3. Record the adverse effects of the different pharmacological therapies reported in the different groups throughout their follow-up.

4. Evaluate the lung function of the different groups at 3 months after discharge, 6 months and 12 months after discharge.

METHODS

a) Location of the study.

National Institute of Respiratory Diseases, Ismael Cosío Villegas México.

Smoking and COPD Research Department.

b) Description of the population:

Inclusion criteria:

1. Over 18 years of age.

2. Active smokers (smoking more than 100 cigarettes in their entire life and having consumed cigarettes in the last 30 days)

3. Hospitalized subjects with acute or chronic lung disease.

4. Signing of informed consent.

Exclusion criteria:

1. Subjects with pharmacological treatment to stop smoking during recruitment or in the last month.

2. Contraindications to the use of pharmacological therapy. (Annex is attached the contraindications for the use of medications)

3. Subjects who cannot maintain follow-up.

Elimination criteria:

1. In an analysis by intention to treat, there will be no elimination of subjects after randomization.

Sample size:

The sample size calculation is carried out by difference between proportions, with a confidence level of 95%, power of 80%, unilateral, with an observed proportion of 65% and an expected proportion of 80% for the combination of pharmacological therapy; 50 subjects are required for each group; If a loss of participants is estimated at 25%, 67 subjects are required for each group. The sample size was carried out in the WinEpi 2006 program.

c) Outcome variables and description of other study variables.

Outcome variable:

-Abstinence: abstinence from tobacco is defined as its suspension 12 months after hospital discharge, corroborated by detection of exhaled carbon monoxide less than 7 ppb and/or detection of cotinine in urine (positive).

-Active smoker: defined as an active smoker who has consumed more than 100 cigarettes in his or her entire life and who has consumed cigarettes in the last 30 days.

-CBT (cognitive behavioral therapy) is a model for treating problematic behaviors that focuses primarily on identifying and changing maladaptive patterns of behavior and thoughts, including problem-solving and coping skills rooted in relapse prevention theory, along with the cognitive restoration of maladaptive thoughts to regulate emotions and is combined with the recommendations of the Clinical Practice Guideline (CPG) for tobacco. (14)

-Acute or chronic lung disease: Acute or chronic lung disease will be considered by medical diagnosis.

-Exhaled carbon monoxide: a value greater than or equal to 7 ppb is defined as positive (subject with active smoking).

-Cotinine in urine: defined as positive (subject with active smoking) positive test (qualitative test)

-Nicotine dependence (Fagerström Questionnaire): mild, moderate and severe.

-Withdrawal symptoms questionnaire.

-Nicotine Craving Questionnaire (Urge to smoke, understood as a physiological and motivational state that drives the desire to smoke tobacco).

-Adverse reactions questionnaire.

-Respiratory symptoms questionnaires (PLATINO).

-Pulmonary function tests (pre- and post-bronchodilator spirometry, carbon monoxide diffusion, and 6-minute walk)

-Beck Anxiety and Depression Questionnaires.

Procedures for collecting information using instruments and data quality control methods. Data Capture.

a)
b) 1-Subject identification (inclusion/exclusion criteria)
c) 2-Signature of informed consent
d) 3-Randomization of the drug (2 groups: a-nicotine patches, b-combination: nicotine patches + bupropion)
e) 4-Start hospitalization treatment
f) - Processes: Medications are given in a personalized way during hospitalization; brief advice is given, and questionnaires and measurements of exhaled CO and cotinine in urine are performed (treatment start day is day 0). The pharmacological treatment given to the subject will be for at least 12 weeks.
g) 5-Monitoring during hospitalization to provide medications

h) 6-Upon discharge, an appointment is made at the Smoking Clinic within the first 14 days of discharge, and anti-smoking treatment for home use and brief advice will be provided.
i) 7-First appointment at the Smoking Clinic
j) - Processes: brief advice; intake of exhaled CO and cotinine in urine). It is scheduled to begin cognitive behavioral therapy (CBT) in a group, which lasts ten sessions, two times a week, with mixed modality (online or in-person).
k) 8-Start CBT in the next two weeks after discharge.
l) 9- Second appointment at the Smoking Clinic at the end of therapy (3 months after discharge)
m) - Processes: brief advice; questionnaires and measurement of exhaled CO and cotinine in urine are performed; pre- and post-bronchodilator spirometry, carbon monoxide diffusion, 6-minute walk.
n) 10-Third appointment at the Smoking Clinic 6 months after discharge:
o) - Processes: brief advice; questionnaires and measurement of exhaled CO and cotinine in urine are performed; pre- and post-bronchodilator spirometry, carbon monoxide diffusion, 6-minute walk.
p) 11-Fourth appointment at the Smoking Clinic 12 months after discharge
q) - Processes: brief advice; questionnaires and measurement of exhaled CO and cotinine in urine are performed; pre- and post-bronchodilator spirometry, carbon monoxide diffusion, 6-minute walk)
r) The information collection will be carried out through the INER RedCAP platform, which has security mechanisms for the data obtained and methods for adequate control. The protocol researchers will carry out data capture.

Results analysis plan.

1- A retrospective analysis was carried out on hospitalized patients with a history of active smoking, with the following characteristics: 40% of the patients evaluated had low dependence on nicotine, and 60% had moderate and severe dependence. Of the patients evaluated, 72% were male, and 28% were female. Proportional allocation is carried out for stratified sampling, Stratified randomization for sex (man and woman), and for low and moderate/severe dependence

2- Statistical analysis methods according to the type of variables: the variables will be analyzed according to their type of distribution and whether they are quantitative or qualitative, by student's t or chi2 as appropriate. A descriptive analysis will be carried out on each of the variables. Subsequently, a comparative analysis will be carried out between the 2 groups included, using ANOVA or Kruskal Wallis, depending on their distribution. The analysis of the main objective will be carried out by intention to treat according to the treatment granted and randomization. Randomization was stratified by level of nicotine dependence and sex. There will be no blinding. The primary outcome will be abstinence at 12 months, and its association with the randomized treatment group will be seen. As a complementary analysis, a per-protocol analysis will be performed according to the treatment received. Finally, through multivariate analysis by logistic regression, abstinence or non-abstinence at one year was analyzed depending on the treatment received, adjusted for the different covariates such as sex, age, smoking rate, and level of dependence.

3-The statistical analysis will be carried out using the STATA V13 statistical package.

ETHICAL CONSIDERATIONS

The type of risk must be considered in accordance with the provisions of Art. 17 of the REGULATIONS of the General Health Law on Health Research:

● Research with minimal risk.

This protocol was approved by the institutional ethics committee under the approval opinion with code C80-23 on November 29, 2023.

Bibliography

1. Makate M, Whetton S, Tait RJ, Dey T, Scollo M, Banks E, et al. Tobacco Cost of Illness Studies: A Systematic Review. Nicotine Tob Res. 2020 Apr 17;22(4):458–65.

2. WHO. World Health Organization, Tobacco [Internet]. World Health Organization; 2022. Available

from: https://www.who.int/news-room/fact-sheets/detail/tobacco

3. World Health Organization. MPOWER : un plan de medidas para hacer retroceder la epidemia de tabaquismo. MPOWER Policy Package Reverse Tob Epidemic. 2008;39.

4. Zoorob RJ, Levine RS, Hennekens CH. Smoking Cessation and Hospitalized Patients: A Missed Opportunity to Avoid Premature Deaths. Ochsner J. 2021;21(1):10–3.

5. Martínez C, Fu M, Castellano Y, Riccobene A, Fernández P, Cabrera S, et al. Smoking among hospitalized patients: A multi-hospitalcross-sectional study of a widely neglected problem. Tob Induc Dis [Internet]. 2018 Jul 30 [cited 2023 Mar 22];16(July). Available from: http://www.journalssystem.com/tid/Smoking-among-hospitalized-patients-a-neglected-problem-A-multihospital-cross-sectional,92927,0,2.html

6. Rigotti NA, Clair C, Munafò MR, Stead LF. Interventions for smoking cessation in hospitalised patients. Cochrane Tobacco Addiction Group, editor. Cochrane Database Syst Rev [Internet]. 2012 May 16 [cited 2023 Mar 22]; Available from: https://doi.wiley.com/10.1002/14651858.CD001837.pub3

7. Leone A, Landini L, Leone A. What is Tobacco Smoke? Sociocultural Dimensions of the Association with Cardiovascular Risk. Curr Pharm Des. 2010 Aug 1;16(23):2510–7.

8. Shamah-Levy T, Vielma-Orozco E, Heredia-Hernández O, Romero-Martínez M, Mojica-Cuevas J, Cuevas-Nasu L, Santaella-Castell JA, Rivera-Dommarco J. Encuesta Nacional de Salud y Nutrición 2018-19. Resultados nacionales. Instituto Nacional de Salud Pública, 2020.;

9. Ferris Wayne G. Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents. Tob Control. 2006 Jun 1;15(3):189–98.

10. Kalkhoran S, Benowitz NL, Rigotti NA. Prevention and Treatment of Tobacco Use. J Am Coll Cardiol. 2018 Aug;72(9):1030–45.

11. Rigotti NA, Regan S, Levy DE, Japuntich S, Chang Y, Park ER, et al. Sustained Care Intervention and Postdischarge Smoking Cessation Among Hospitalized Adults: A Randomized Clinical Trial. JAMA. 2014 Aug 20;312(7):719.

12. Sørensen LT. Wound Healing and Infection in Surgery: The Pathophysiological Impact of Smoking, Smoking Cessation, and Nicotine Replacement Therapy A Systematic Review. Ann Surg. 2012 Jun;255(6):1069–79.

13. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking Cessation Reduces Postoperative Complications: A Systematic Review and Meta-analysis. Am J Med. 2011 Feb;124(2):144-154.e8.

14. A Clinical Practice Guideline for Treating Tobacco Use and Dependence: 2008 Update. Am J Prev Med. 2008 Aug;35(2):158–76.