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ORIGINAL CONTRIBUTION

EFFECT OF N-ACETILCYSTEINE ON BRONCHIECTASIS IN A REAL-LIFE STUDY. DATA FROM THE RIBRON REGISTRY

Short title: Effect of N-acetilcysteine in bronchiectasis

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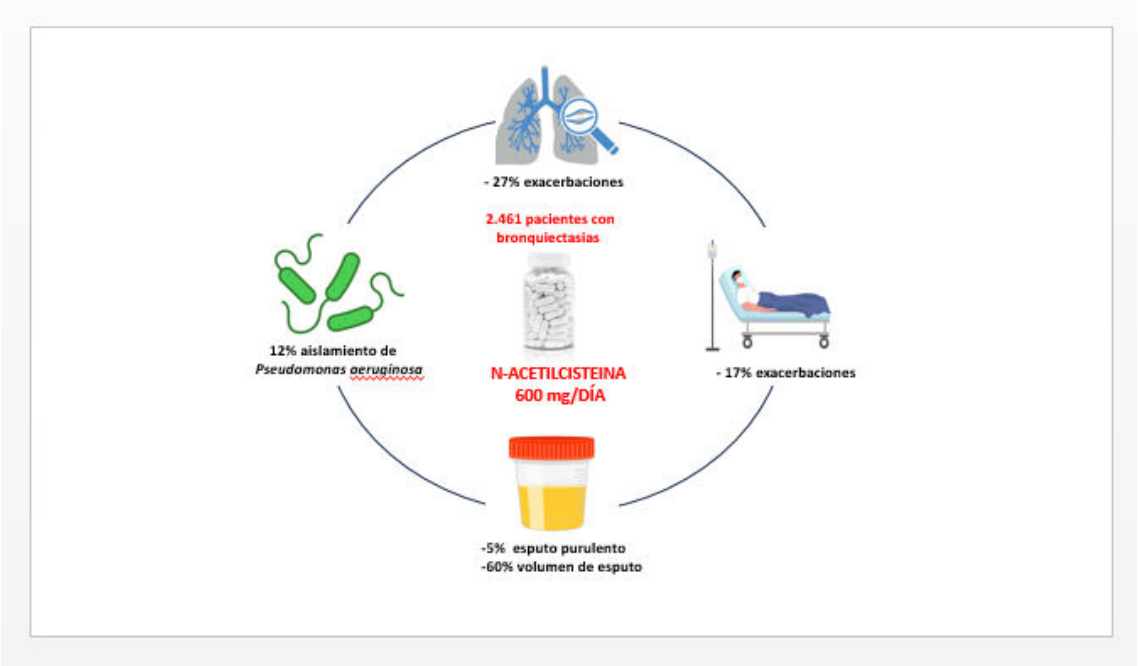
Graphical Abstract



ABSTRACT

Introduction. There is scarce information about the most used mucolytic drug in bronchiectasis – N-acetylcysteine (N-AC). Our objective was to analyze the effect of N-AC with respect to some outcomes in bronchiectasis

Methods. Ambispective, longitudinal, observational, multi-center (43 centers) study of a cohort of 2,461 adult patients diagnosed with bronchiectasis. Those patients treated in a stable situation with at least 600 mg/d of N-AC (368; 15%) for at least 6 months were compared with patients not receiving this treatment. The variables analyzed and compared were those available two years before and after treatment. ANCOVA analysis was used to analyze the effect of N-AC as the intergroup difference of the basal intragroup difference for each variable, adjusted for relevant covariables.

Results.The N-AC group showed a full adjusted improvement of 27% in exacerbations, 17% in hospitalizations, and 31% in total exacerbation rates compared with the no-N-AC group. Moreover, a decrease in the volume of sputum production of 59.7% was observed as well as. a decrease of 12% of patients with bronchial infection by PA. The use of 1,200 mg/d (n=116) resulted in only a mild, albeit improvement in the exacerbation rate compared with the use of 600 mg/d (11% higher). Both doses were well tolerated.

Conclusion. N-AC (in most cases at a dose of 600 mg/d) is safe and effective and sufficient to reduce both the number of exacerbations and hospitalizations and the purulence and volume of sputum, as well as the isolation rate of PA. in patients with bronchiectasis

Keywords: Bronchiectasis, mortality, exacerbations, hospitalizations, *Pseudomonas aeruginosa.*

INTRODUCTION

Most of the international guidelines on airway diseases with excessive production of bronchial mucus and multiple exacerbations especially in those patients with airway comorbidities recommend the use of mucolytics, given the relationship between mucous hypersecretion (especially if it is abundant and/or purulent) and various factors associated with a poor prognosis in these patients (1-6).

Among the mucolytics, N-acetylcysteine (N-AC) has been one of the most studied and used, especially in chronic obstructive pulmonary disease (COPD) (7) with chronic bronchitis and in cystic fibrosis (CF) (8), on account of its mucolytic activity and its ability to reduce the viscosity of sputum and thus promote its expulsion, as well as its antioxidant capacity at high doses (9).

Bronchiectasis is, after COPD and asthma, the third most common chronic inflammatory disease of the airway (10). It is clinically characterized by the hyperproduction of bronchial secretions, with a habitual increase in their viscosity and purulence (9), associated with an excess of exacerbations with an infectious profile that worsens the patient's prognosis (6). In fact, the color of the sputum in these patients is one of the most important biomarkers of the severity of bronchiectasis, along with the presence of exacerbations and the response to treatment (11).

Although the existing scientific evidence on the effect of N-AC in patients with bronchiectasis is very poor, all guidelines on this disease recommend its use (among other mucolytics) in those patients with abundant bronchial hypersecretion, owing to the scarcity of its adverse effects (1-3). Very few studies to date have specifically analyzed the effect of N-AC on the number and severity of exacerbations in patients with bronchiectasis not due to CF. Of particular note in this respect is the small randomized clinical trial by Qian et al (12) (161 patients) with an active group treated with 1,200 mg/d of N-AC, which concluded with a reduction in exacerbations and the time until the first exacerbation at 12 months. In another small study, 24 patients were randomized to 2,400 mg/d of N-AC for 6 weeks, with improvements in some domains of the quality of life but, most importantly, without any excess of adverse effects, despite the high dose used (13).

RIBRON (14,15) is the Spanish registry of bronchiectasis, which has collected data from more than 2,600 patients diagnosed with bronchiectasis by high-resolution chest tomography (HRCT) and clinical findings compatible with these radiological findings, followed for a median of 7 years. All the data regarding all the treatments received and the doses used in both the acute and stable phases were collected at their start and end dates. Taking advantage of the characteristics of RIBRON, our objective was to analyze, ~~in a study with real-life methodology~~, the effect of the use of N-AC for at least 6 months on the rate of exacerbations and hospitalizations in patients with bronchiectasis.

METHODS

Study Design

Ambispective, longitudinal, observational, multi-center (43 centers from all over Spain) study of a cohort of adult patients (at least 18 years old) diagnosed with bronchiectasis by means of HRCT, with related clinical symptoms derived from the Spanish Bronchiectasis Registry (RIBRON) (14,15). We used a real-life methodology since the study is based on usual clinical practice following the national recommendations

Patients

Data was available on 2,630 patients included in the registry from February 2015 to December 2019. Inclusion criteria were: complete clinical, functional, etiological, analytical, and therapeutic data available at entry, in conditions of clinical stability, as well as complete data on exacerbations and hospitalizations during the first and second year of follow-up and before starting the treatment with N-AC. The main criterion for exclusion was a diagnosis of cystic fibrosis (CF).

The local ethics committee affiliated with the registry (number: 001-2012. Josep Trueta.Girona) approved the study and all the patients gave their written informed consent in their corresponding participating center.

Variables and definitions

The following variables were used for the purposes of this study: baseline general and anthropometric data; etiology; comorbidities (Charlson Index); lung function; treatments; clinical, analytical, radiological and microbiological data; the number and severity of incident exacerbations, and multidimensional severity scores (FACED, E-FACED and BSI) (16-18). ~~Finally, the Charlson Index was used to quantify comorbidities.~~

An exacerbation was defined (when the registry was created) as a worsening of the typical symptoms of bronchiectasis: cough, dyspnea, hemoptisis, increase in the volume or purulence of the sputum, chest pain, and sibilance with an evolution of more than 24 hours for which antibiotic treatment

was required. An exacerbation was considered mild-moderate when the patient needed oral antibiotics, and severe in cases of hospital admission or when intravenous antibiotic treatment was required in either a hospital or a home setting (19). Exacerbator patients were defined as those with at least three exacerbations per year or two mild-to-moderate exacerbations plus at least one hospitalization (20,21). Chronic bronchial infection (CBI) was defined as the presence of three or more consecutive cultures positive for the same potentially pathogenic microorganisms (PPM) (22).

Patients were divided into two groups **(Figure 1):** Those taking at least 600 mg per day (or 1,200 mg per day) of N-AC during at least 6 months prescribed in a stable phase, and a control group without N-AC. Data related to the two years before the initiation of N-AC treatment and the two subsequent years were extracted from both groups. The control group included all patients with no N-AC treatment and data from two years after and before the optimal database point with available data.

Statistical analysis

Data were tabulated using the mean ± standard deviation or median (interquartile range) for quantitative data that, respectively, followed or did not follow a normal distribution. The normality of the distribution was analyzed using the Kolmogorov-Smirnov test. The qualitative data were tabulated according to the percentage with respect to the total value. Correlations between quantitative variables were established using Pearson test or Spearman tests, depending on the variable distribution.

Since, as expected, the baseline data were different in those patients taking and not taking N-AC, this difference was taken into account when calculating the effect of N-AC. Therefore, the effect of N-AC was the intergroup difference of the basal intragroup difference for each variable. Intra-group baseline characteristics were assessed using the t-student t or chi-square test. Inter-group final differences were assessed in a similar way, and each intra-group difference over time was assessed for each variable by ANCOVA analysis, taking into account the adjusted variables, especially the differences in baseline data

(Figure 2). The statistical package SPSS Inc. 20 was used. A P value < 0.05 was considered statistically significant.

RESULTS

~~Observational study of historical cohorts~~. Of the 2,630 patients initially recruited, 169 were excluded due to CF. Therefore, the analysis was performed on the remaining 2,461 patients. Of these, 368 (15%) took N-AC for at least 6 consecutive months with treatment initiated outside an exacerbation process, according to their physicians, following the current national bronchiectasis guidelines. Of these 368 patients, the same information was collected retrospectively from the two years prior to the start of taking N-AC. Of these, 252 (68.5%) took 600 mg per day while 116 took 1,200 mg/d (600 mg/12 hours) (31.5%).

In **Table 1**, as expected, it can be seen that those patients who were started on N-AC had a more serious clinical disease profile and more exacerbations, amounts of sputum produced per day, Chronic bronchial infection (CBI) by potentially PPM and use of other treatments than those who were not prescribed N-AC (maintenance of a high number of exacerbations or sputum despite baseline treatment).

Effect on exacerbations/hospitalizations

The annual rate of exacerbations and hospitalizations in the two years prior to prescribing N-AC were 1.26 (1.39) and 0.53 (1.3) respectively, while in the active group (with N-AC) they were 1.58 (1.8) and 0.58 (1.3), respectively. In the two years following prescription they were 0.77 (1.3) / year and 0.17 (0.13) / year respectively.

As a consequence of the different initial profiles of both groups, **Table 2** shows how the differences both within and between groups remained significant, despite taking into account the baseline values of exacerbations and adjustment for differences in clinically significant confounding variables, based on the opinion of the researchers and the clinical information available in the literature.

Effect on sputum purulence and volume

Figure 3 shows how the degree of purulence and the amount of sputum decreased significantly in those patients who were prescribed N-AC compared with those who not. Patients with usual mucopurulent or purulent sputum decrease by 5% and those with less than 20 cc of daily volume decreased by 50% taken into account the differences into the non-N-AC group

Effect on bronchial infection by Pseudomonas aeruginosa

Figure 4 shows that 35.2% of those patients receiving N-AC presented CBI by *P. aeruginosa (PA)* versus only 13.4% of those not receiving N-AC. However, during the 2 years following the initial treatment, only 20.3% of the N-AC patients continued with CBI by PA, while nearly the same number of patients continued with CBI by PA in the non-N-AC group. Therefore, there was a decrease of 17.9% in patients with CBI by PA within those receiving N-AC, compared with the non-N-AC group.

Effect of 1,200 mg/d N-AC versus 600 mg/d

Although the usual and most commonly prescribed dose was 600 mg/d, approximately one-third of the patients (n=116) were prescribed a dose of 600 mg/12 hours (1,200 mg/d). The effect was a significant decrease in exacerbation rates (Only 600 mg: full adjusted differences: -0.21 (-0.14 to -0.31) for the 600 mg group, and -0.31 (-0.22 to -0.44) in the 1,200 mg/d group (inter-group P: 0.019), but no differences in hospitalizations were seen: -0.14 (-0.06 to -0.16) vs -0.19 (-0.09 to -0.19) **Figure 5.** Likewise, no additional improvements were observed in microbiological changes in respiratory samples, the decrease in exacerbation rates, or the degree of sputum purulence with respect to the 1200 mg group when compared with the 600 mg/d group. In general, the tolerance was excellent, with no significant adverse effects reported in any patient, independently of the dose used.

DISCUSSION

According to our results in this real-life study based on national bronchiectasis guidelines, the addition of N-AC to those patients with an increase in their exacerbations despite the prescribed treatment leads to a clinically relevant and significant decrease in the annual rate of exacerbations, as well as in sputum purulence and the isolation of *P. aeruginosa*. At the dose of 1,200 mg/d of N-AC, no clinically significant advantages were obtained, except for an even greater decrease in mild-to-moderate exacerbations. No patient presented significant adverse effects with N-AC, regardless of its dose.

N-AC is probably the most widely used mucolytic in bronchiectasis, despite the fact that the existing evidence on this subject is scarce and the optimal dose and its safety are unknown (23). This limited evidence, confined to three studies (12,13,24), one of them a small clinical trial, indicates that N-AC may be beneficial in reducing exacerbations in patients with bronchiectasis. In our study, the first with real-life methodology and the most extensive to date, we concluded that with the use of 600 mg/d there is indeed a decrease of between 17-27% in exacerbations and hospitalizations, which translates into something more than 30% in the overall group. Therefore, our findings confirm the results already published by other authors.

Since it has been proven that N-AC, in addition to having mucolytic effects, also has anti-infective and antioxidant effects (23-26), we studied its behavior against the presence of *P. aeruginosa* bronchial infection (a key bacteria in the prognosis of patients with bronchiectasis), with a very significant decrease in those with N-AC. Likewise, sputum purulence, measured according to Murray's criteria, also decreased (27).

Furthermore, a group of patients were treated with 1,200 mg/d of N-AC. These patients presented an even greater number of exacerbations before entering the study. The effect of this high dose was very safe but moderate, only showing a significant but small decrease in the number of non-serious exacerbations compared to the 600 mg/d group (-0.31 vs -0.42; p=0.046). These results are in agreement with those observed in the small randomized clinical trial

of Jayaram et al (13) where the use of 2,400 mg/d of NAC was safe and even improved some dimensions of the quality of life of the participants

Among the strengths of this study is that it is longer, with a greater number of variables analyzed, a greater number of patients included, and a methodology close to clinical practice (real-life study), based on the prevailing national guidelines. Although it is obvious that other treatments such as inhaled antibiotics or macrolides (28,29) have also shown a decrease in exacerbations, both treatments were treated as adjustment variables, in order to adjust their effects from the results obtained. Other variables were similarly used, to isolate as far as possible the effect of the drug being studied, in this case N-AC. Among the study's limitations, without a doubt the most important is that it is not a randomized study and that the characteristics of bronchiectasis in different parts of the world are very diverse (30,31), so these results would have to be confirmed in series of different patients from different countries. Moreover this is a real-life study therefore the control of some variables could not be optimal

In conclusion, N-AC (in most cases at a dose of 600 mg/d) is safe and effective in reducing both the number of exacerbations and hospitalizations, as well as sputum purulence and the isolation rate of *P. aeruginosa*. Further large studies in the form of clinical trials are needed, including investigation of the possible additional advantage of N-AC at higher doses, its position in the current algorithm (1-3) of treatment and the possibility of new drugs for bronchiectasis (32-33) in the next future given the safety of the product.

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Contributions:

Study Design: MAMG and GO,

Data acquisition: MAMG,GO, CO, RG,MGC,LM,OS,RG,RM,JRL,EB,CP,JLR and DR.

Data interpretation and writing the manuscript: All authors.

All authors critically reviewed the manuscript, and approved its final submitted, version

Competing interests: RM is the recipient of a Juan Rodés grant, supported by the Instituto de Salud Carlos III (ISCIII [JR21/00051]). All other authors declare no competing interests.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

Yes

If yes; please provide name of the ethical committee approving these experiments and the registration number. :

Josep Trueta-001-2012

If yes; please confirm authors compliance with all relevant ethical regulations. :

Yes

If yes; please confirm that written consent has been obtained from all patients. :

Yes

3. Does your study include a clinical trial?:

No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

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Table 1. Comparative characteristics of the N-AC and no N-AC groups

*Exacerbation rate (previous two years) in steady-state situation

N-AC: N-acetylcysteine; COPD: Chronic obstructive pulmonary disease; BSI: Bronchiectasis Severity Index; C-RP: C-reactive protein; CBI: Chronic bronchial infection; LABA: long-acting beta adrenergic; HS7%. Hypertonic saline at 7%

Variable	**N-AC (n=368)**	**No N-AC (n=2,093)**	P value
Age, yrs	65 (11.5)	64.4 (16.4)	0.768
Gender (% women)	68%	63%	0.699
Pack.year	32.4 (28.1)	26.4 (22.8)	0.232
Daily sputum quantity ml (>20 ml/day)	78.9%	21.1%	0.001
Usual sputum purulence	35.2%	21.1%	0.001
COPD, %	11.6%	8.4%	0.256
Asthma, %	7.8%	9.1%	0.343
Charlson Index	1.8 (1.4)	1.8 (1.4)	0.912
Post-infectious etiology, %	37.5%	38.8%	0.911
Idiopathic etiology, %	19.6%	18.4%	0.822
FACED	2.1 (1,8)	1.9 (1.8)	0.345
EFACED	2.6 (1.9)	2.4 (1.9)	0.389
BSI	6.6 (1.9)	6.4 (1.9)	0.412
FEV1%, predicted	77.7 (24)	74 (26.4)	0.593
Dyspnea mMRC	2.2 (1)	2.2 (1)	0.498
Pulmonary lobes affected	2.8 (1.4)	2.71 (1.4)	0.232
C-RP	6.6 (12)	4.8 (18.5)	0.121
Fibrinogen (mg/ml)	438 (125)	411 (146)	0.146
Platelets x 10^3 cells	258 (78)	247 (79)	0.223
CBI by PA, %	35.2%	13.4%	0.001
CBI by other MPP, %	43%	36%	0.025
Previous exacerbations/yr*	1.58 (1.8)	1.26 (1.3)	0.013
Previous hospitalizations/yr*	0.59 (1.3)	0.53 (1.3)	0.025
Total previous exacerbations/yr*	2.21 (2.5)	1.78 (2.1)	0.036
Exacerbations/year	0.77 (1.3)	1.49 (1.5)	0.027
Hospitalizations/yr	0.17 (0.5)	0.44 (0.4)	0.017
Total exacerbations	0.94 (0.7)	1.93 (0.8)	0.031
Inhaled corticosteroids, %	48.6%	49.7%	0.782
Macrolides, %	10%	5.9%	0.045
Inhaled antibiotics	21%	14%	0.023
Physiotherapy, %	31.5%	29.7%	0.473
LABA; %	56%	31%	0.042
HS7%; %	7%	7%	0.012
Death, %	17%	21%	0.267

Table 2. Adjusted effect of NA-C on yearly exacerbation and hospitalization rates

*Adjusted by initial dose of N-AC, gender, age, baseline FEV1, previous exacerbations and hospitalizations, *Pseudomonas aeruginosa* infection, presence of COPD or asthma, Charlson Index, BSI score, sputum purulence, use of bronchodilators, inhaled corticosteroids, and inhaled antibiotics or macrolides.

	2 previous years (per year)			2 subsequent years (per year)					
Variable	N-AC	No N-AC	Inter-group differences (CI95%)	N-AC	No N-AC	Intra-group raw differences (CI95%)	Crude difference of differences	Fully adjusted differences*	P (fully adjusted differences)
Exacerbations/year	1.58 (1.3)	1.26 (1.8)	0.32 (0.61 to 0.44)	0.77 (1.3)	1.49 (1.5)	0.72 (0.26 to 1.12)	-0.40 (-0.55 to -0.27)	**-0.27** (-0.20 to 0.31)	0.003
Hospitalizations/year	0.58 (1.3)	0.53 (1.3)	0.05 (0.25 to 0.44)	0.17 (0.5)	0.44 (0.4)	0.27 (0.7 to 0.47)	-0.22 (-0.11 to -0.35)	**-0.17** (-0.10 to -0.23)	0.022
Total exacerbations/year	2.10 (2.5)	1.49 (2.1)	0.37 (0.62 to 0.88)	0.94 (0.7)	1.93 (1.5)	0.99 (0.13 to 0.44)	-0.62 (-0.92 to -0.29)	**-0.31** (-0.21 to -0.38)	0.021

FIGURE LEGENDS

FIGURE 1. Flow-chart of the study. Prescription, doses and duration of N-acetylcysteine.

Figure 1

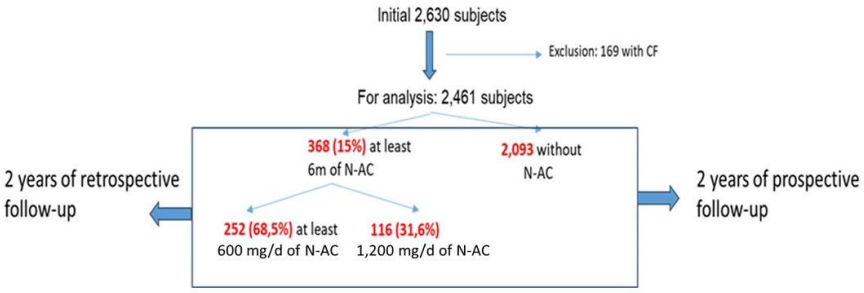

FIGURE 2. Time line of the study period in both groups, variables studies for comparisons.

Figure 2

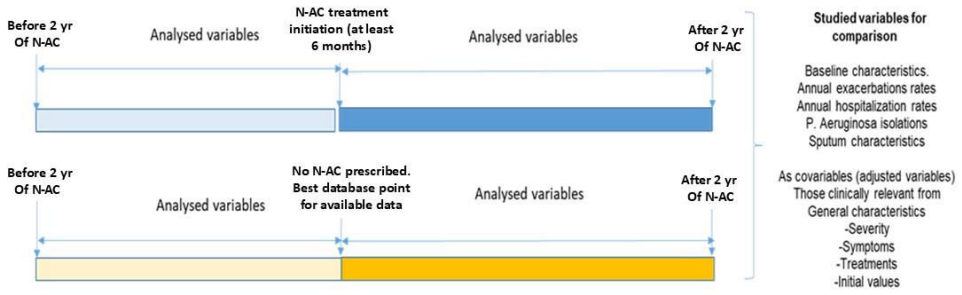

FIGURE 3. Effect of N-AC on exacerbations and hospitalizations, taking into account the yearly progression of the exacerbation/hospitalization rate.

Figure 3

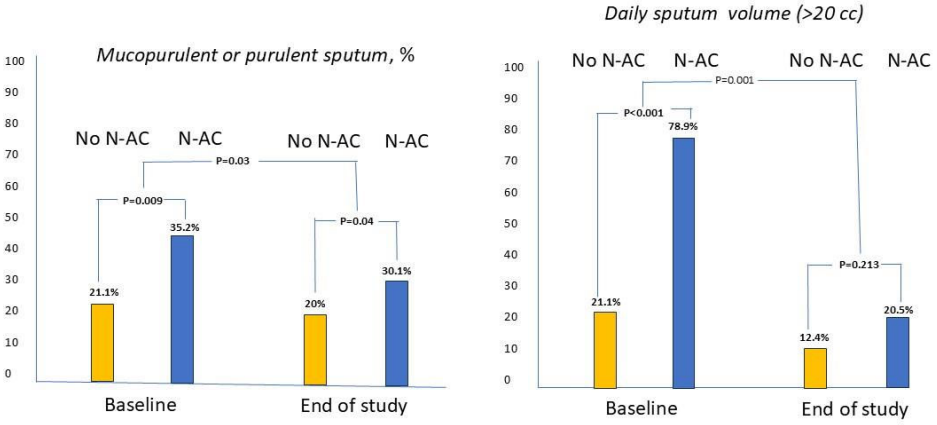

FIGURE 4. Effect of N-AC on the degree of purulence and the amount of sputum.

Figure 4

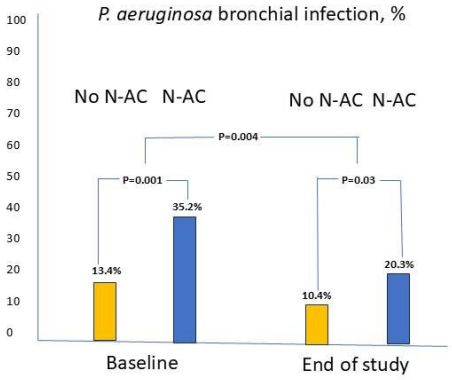

FIGURE 5. Effect of N-AC on the *Pseudomonas aeruginosa* bronchial infection

Figure 5