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Inhaled bronchodilators use and clinical course of adult inpatients with Covid-19 pneumonia in Spain: A retrospective cohort study☆

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ABSTRACT

Background: In the current coronavirus health crisis, inhaled bronchodilators(IB) have been suggested as a possible treatment for patients hospitalized. Patients with evidence of Covid-19 pneumonia worldwide have been prescribed these medications as part of therapy for the disease, an indication for which this medications could be ineffective taken on account the pathophysiology and mechanisms of disease progression.

Objective: The main objective was to evaluate whether there is an association between IB use and length of stay. Primary end points were the number of days that a patient stayed in the hospital and death as a final event in a time to event analysis. Pneumonia severity, oxygen requirement, involved drugs, comorbidity, historical or current respiratory diagnoses and other drugs prescribed to treat coronavirus pneumonia were also evaluated.

Methods: A descriptive, observational, cross-sectional study was performed in this tertiary hospital in Madrid (Spain). Data were obtained regarding patients hospitalized with Covid-19, excluding those who were intubated. The primary and secondary outcomes such as duration of hospitalization and death were compared in patients who received IB with those in patients who did not.

Results: 327 patients were evaluated, mean age was 64.4 ± 15.8 years. Median length of hospitalization stay was 10 days. Of them 292 (89.3%) overcame the disease, the remaining 35 died. Patients who had received IB did not have less mortality rate (odds ratio 0.839; 95% CI: 0.401 to 1.752) and less hospitalization period when compared with patients who did not received IB (odds ratio 1.280; 95% CI: 0.813 to 2.027). There was no significant association between IB use and recovery or death. Hypertension and diabetes were the most common comorbidities. The prevalence of chronic respiratory disease in our cohort was low (21.1%). Anticholinergics were the IB more frequently prescribed for Covid-19 pneumonia. Better response in patients treated with inhaled corticosteroids was not observed.

Conclusion: Off-label indication of inhaled-bronchodilators for Covid-19 patients are common in admitted patients. Taken on account our results, the use of IB for coronavirus pneumonia apparently is not associated with a significantly patient’s improvement. Our study confirms the hypothesis that inhaled bronchodilators do not improve clinical outcomes or reduce the risk of Covid-19 mortality. This could be due to the fact that the virus mainly affects the lung parenchyma and the pulmonary vasculature and probably not the airway. More researches are necessary in order to fill the gap in evidence for this new indication.

1. Background

Therapeutic approach for Covid-19 worldwide has been primarily supportive therapy and, to date, there is no specific treatment. The fact that it is a new disease leads to the lack of approved medications for this indication. To date, only remdesivir has been authorized by the FDA via emergency use authorization. [1] As a consequence, a large number of patients around the world have received off-label treatments since there...
is currently no clinical evidence supporting the efficacy and safety of medications used against Covid-19 [2].

Increasing the understanding of the coronavirus disease is essential in order to initiate timely and targeted therapy. It is known that it has three consecutive stages [3]: the early stage characterized by flu-like symptoms and subsequently viral pneumonia, followed by pulmonary inflammation, coagulopathy and increased levels of inflammatory biomarkers associated with the development of acute respiratory distress syndrome. Finally, the third stage of the disease with an increased risk of lung fibrosis.

In this scenario, inhaled bronchodilators (IB) have been suggested as a possible treatment. According to the WHO’s Anatomical Therapeutic Chemical (ATC) Classification, IB include inhaled adrenergics, anticholinergics and corticosteroids.[4]

Thousands of hospitalized patients with evidence of Covid-19 pneumonia worldwide have been prescribed these medications as part of treatment for the disease. [5] However, taking into account the pathophysiological mechanism of the disease previously exposed, with development of hyperinflammation hypercoagulability and potential fibrosis, the use of these drugs may be ineffective given the absence of airway pathology.

The use off-label of IB for hospitalized patients is not new. Thus, recent studies have shown that nearly half of them are prescribed for unapproved indications for which there is a very little scientific evidence on its effectiveness [6]. To date there are no robust clinical trials proving their efficacy for most of these indications, including pneumonia caused by coronavirus.

In this unexpected context, there is no way of knowing if Covid-19 patients treated with IB had been benefited or were injured as they were not compared with a concurrent control group. Thus, it is impossible to differentiate drug related adverse effects from disease manifestations in the absence of a control group.

In addition, among IB, those containing corticosteroids are frequently prescribed. Regarding these drugs, in Covid-19 patients published studies have yielded conflicting results concerning anti-inflammatory effects of systemic corticosteroids; both beneficial [3,7,8,9] and harmful [10,11] effects have been reported. A preliminary analysis from a large, multicentre, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients with severe Covid-19 randomized to receive systemic dexamethasone had a reduced rate of mortality compared to those who received standard of care. [12] Nevertheless, to date, there is no information on whether IC for Covid-19 patients with pneumonia constitutes a protective or harmful factor. Although scarcely, some researchers are already carrying out studies of this type. [13,14].

Given this situation, the following study was undertaken. We hypothesised that the use of IB for Covid-19 patients could be useless taken on account the pathophysiology and mechanisms of disease progression.

2. Material and methods

We conducted this study in Madrid, the epicentre of the pandemic in Spain, in one of the hospitals with the largest number of patients admitted with Covid-19. A descriptive, observational, cross-sectional study was performed in this tertiary hospital (1300 beds) on March 24, 2020. Physicians prescribed therapies to Covid-19 inpatients using a computerised physician order entry (CPOE) programme where they also record the diagnosis and severity. A community-based clinical information programme available in Spain (Horus®) linked to these CPOE programmes are used for hospitalized patients. This programme allows physicians and pharmacists in hospitals to access patients’ information of comorbidity and drug indications, including IB, prior to admission, creating a longitudinal electronic health record of clinical and pharmacologic data.

Treatments of all admitted adults who tested positive were reviewed. Test result for Covid-19 virus from analysis of nasopharyngeal or oropharyngeal swab samples were obtained during hospitalization. These tests were carried out by hospital health personnel and results were registered by physicians in the Electronic Medical Record (EMR).

Although a treatment protocol was established at the centre for these patients, the decision to prescribe, including IB, was left to the discretion of the treatment team for each individual patient.

2.1. Study population

Adult patients diagnosed of Covid-19 at admission were included in the study. As exclusion criteria we considered Covid-19 patients admitted to critical care units.

The institutional review board of our center approved this analysis under an expedited review.

2.2. Aim of the study

The main objective was to evaluate whether there is an association between IB use and length of stay. Pneumonia severity, oxygen requirement, involved drugs, comorbidity and current respiratory diagnoses, other drugs prescribed to treat coronavirus and whether IB had been initiated at admission or before admission were also evaluated.

2.3. Data source

From the clinical data warehouse, we obtained data from all prescription events of hospitalized patients with Covid-19 under IB treatment (according to the WHO’s ATC classification [4]) who presented respiratory illness, which was defined as a resting oxygen saturation of less than 94% being treated with IB. The data obtained included patients’ demographic details, medication administration data, historical and current medication lists, historical diagnoses, oxygen requirements.

2.4. Statistical analysis

2.4.1. Data management

A database was designed to reflect the case report content form, in which a data entry matrix with possible ranges or values was established, along with the various consistency rules between variables. The quality of information received through exploratory analysis was aimed at detecting discrepancies in the values, out-of-range or missing values. An exploratory analysis also provided information on the distribution of the main variables to be studied and provided guidance on possible transformations.

2.4.2. General considerations

The mean, SD, median, maximum, minimum, and 25% and 75% quartiles were included. For the categorical data, the frequency distributions (absolute and relative) were presented. In addition, 95% CIs were calculated when appropriate. The statistical analysis was performed using SAS9.3 (SAS Institute, Cary, North Carolina, USA).

The median length of hospitalization was 10 days, that’s the reason why we chose this value when dichotomizing the variable.

3. Results

3.1. Characteristics of the cohort

The pharmacotherapy of 327 hospitalized patients with Covid-19 who were admitted to the hospital the day we carried out the cross section was analyzed. Of them 292/327 (89.3%) overcame the disease, the remaining 35 died. At the time of data cut-off on March 24, 2020, a total of 124 patients were exposed to IB of which 44 contained IC (35.5%) (Fig. 1).
Patients were predominantly male (57%). Men and women death rate were 65.7% and 34.3%, respectively. Mean age was 64.4 ± 15.8 years and length of hospitalization stay was 13.2 ± 8.3 days. The distribution of the patient’s baseline characteristics according to IB exposure is shown in Table 1.

Regarding patients who had received IB, they did not have less hospitalization period when compared with patients who did not received IB (odds ratio 1.280; 95% CI: 0.813 to 2.027) (Table 2). Also, mean length of stay was not different comparing both groups (Fig. 2). Finally, no differences were observed comparing mortality in patients receiving IB with not receiving IB (9.7% vs. 11.3%, p = 0.639).

At the same time, among patients receiving IB, comparing those treated and not treated with IC, no differences were observed in the length of stay (Table 3). Specific treatment for Covid-19 according to inhalers prescription was also analyzed (Table 4).

We also analyzed the coronavirus pneumonia severity of patients using inhalers compared with those who did not. When using the CURB-65 pneumonia severity score [15] we found that 78/327 (23.8%) suffered severe pneumonia symptoms. Moreover, better results for patients with low and high risk of mortality according to the CURB-65 were observed (Fig. 3).

As for the oxygen needs, we observed that the vast majority of

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**Table 1** Characteristics of Covid-19 patients receiving or not bronchodilator inhalers.

| Characteristic                        | Total (N = 327) | % | Bronchodilator inhalers (N = 124) | % |
|---------------------------------------|-----------------|---|-----------------------------------|---|
| **Age**                               |                 |   |                                   |   |
| <40 years                             | 28/327          | 8.5% | 6/28                             | 4.8% |
| 40–59 years                           | 87/327          | 26.5% | 27/87                             | 21.6% |
| 60–79 years                           | 157/327         | 47.9% | 71/157                            | 56.8% |
| ≥80 years                             | 56/327          | 17.1% | 21/56                             | 16.8% |
| **Comorbidity**                       |                 |   |                                   |   |
| Comorbidity                           | 229/327         | 69.8% | 92/125                            | 73.6% |
| Hypertension                          | 90/229          | 39.3% | 59/92                             | 54.3% |
| Obesity                               | 25/229          | 10.9% | 11/92                             | 11.9% |
| Cancer                                | 32/229          | 14%  | 13/92                             | 14.1% |
| Cardiovascular                        | 63/229          | 27.5% | 26/92                             | 28.2% |
| Diabetes                              | 61/229          | 26.6% | 25/92                             | 27.2% |
| Other                                 | 92/229          | 40.2% | 25/92                             | 27.2% |
| **Respiratory illness at baseline**   |                 |   |                                   |   |
| COPD                                  | 42/69           | 60.9% | 27/43                             | 62.8% |
| Asthma                                | 13/69           | 18.8% | 12/43                             | 2.8% |
| OSAS                                  | 13/69           | 18.8% | 11/43                             | 2.5% |
| Other                                 | 10/69           | 14.5% | 10/43                             | 2.6% |

COPD—Chronic obstructive pulmonary disease. OSAS—Obstructive sleep apnea syndrome.
This study shows that a high percentage (37.8%) of Covid-19 admitted patients received IB during hospitalization. The risk of increased hospitalization period or death was not significantly lower among patients who received IB than among those who did not (odds ratio 0.839; 95% CI: 0.401 to 1.752 and odds ratio 1.280; 95% CI: 0.813 to 2.027 respectively). The lack of efficacy could be explained as Covid-19 predominantly causes inflammation in lung parenchyma and in vascular system over conducting airways, the target of IB.

Our findings do not support the use of these drugs since there are not of randomized clinical trials (RCT) proving their efficacy yet. RCT is the best way to prove whether benefit can be attributed to any new treatment, minimizing confounding bias.

To our knowledge, this study is the first that evaluates the degree of IB prescribed for coronavirus respiratory illness use as there exists no other data available to compare with.

As we noted in the introduction, previous researches have already proven that IB are widely used off-label for respiratory infections with lack of evidence [2,16,17]. Moreover, it is known that the use of drugs for unapproved conditions is not always beneficial, in some cases they have been associated with higher rate of ADEs [2,18] and avoidable costs [19,20,21]. Our results suggest a need for more IB monitoring in Covid-19 pneumonia in order to identify their effects not only in terms of clinical efficacy, but safety.

As in other observational cohorts, our study reveals that patients with coronavirus had numerous comorbidities, the most common of which were arterial hypertension and diabetes. [22,23,24,25,26,27] Nevertheless, we did not find differences between patients treated and not treated with IB in terms of comorbidity. Surprisingly, the prevalence of chronic respiratory disease among patients with Covid-19, in agreement with other researchers [2] in our cohort was low (21.1%).

In this analysis, consistently with previous published studies [20] we detected a high proportion of unapproved use of anticholinergics. In addition, our study could not prove that IC were associated with clinical improvement in Covid-19 patients.

Stratifying by severity and inhaled therapy, we did not find in our observational cohort that patients treated with IB showed a better prognosis for the same stratum of severity.

### Table 2
Association between inhaled bronchodilators use and the endpoint of discharge or death and the hospitalization period.

| Analysis | Patients receiving inhaled bronchodilators (N = 124) | Patients not receiving inhaled bronchodilators (N = 203) | OR (95% CI) |
|----------|---------------------------------------------------|---------------------------------------------------|-------------|
| Duration of hospitalization category: | | | |
| <10 days | 56/124 (45.2%) | 103/203 (50.7%) | 1.284 (0.813-2.027) |
| >10 days | 68/124 (54.8%) | 100/203 (49.3%) | 1.230 (0.848-1.796) |

### Table 3
Inhaled corticosteroids prescription in Covid-19 patients according to length of hospitalization and the final endpoint (discharge or death).

| Analysis | Treated with inhaled corticosteroids N = 44 | Not treated with inhaled corticosteroids N = 80 | OR (95% CI) | p value |
|----------|--------------------------------------------|-------------------------------------------------|-------------|---------|
| Duration of hospitalization category: | | | | 1.111 (0.521-2.271) | 0.848 |
| <10 days | 18/44 (40.9%) | 37/80 (46.3%) | | |
| >10 days | 26/44 (59.1%) | 43/80 (53.7%) | | |
Fig. 3. Association between bronchodilator inhalers use and the composite end point of shortening admission period and death according to clinical conditions: IB: inhaled bronchodilators.

The assessment of IB off-label prescription in a setting not previously described renders clinical relevance and strength to this study. However, it is limited by weaknesses inherent in a cross-sectional and single-centre study. Other limitations may be that there could have been patients who met inclusion criteria but were not assessed because of missing data for some variables and potential for inaccuracies in the electronic health records such as lack of documentation of coexisting illness for some patients. Finally, the response to systemic corticosteroids could interfere with the results, although very few patients were treated and existed in both groups, whether or not they received IB.

5. Conclusion

Off-label indication of inhaled-bronchodilators for Covid-19 patients are common in admitted patients. Taken on account our results, the use of IB for coronavirus pneumonia apparently is not associated with a significantly patient’s improvement. Our study confirms the hypothesis that inhaled bronchodilators do not improve clinical outcomes or reduce the risk of Covid-19 mortality. This could be due to the fact that the virus mainly affects the lung parenchyma and the pulmonary vasculature and probably not the airway.

Even though our study do not support this use for IB, it proves that more researches are necessary in order to fill the gap in evidence for this new indication.

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CRediT authorship contribution statement

Elena Villamanán: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing. Carmen Sobrino: Data curation, Writing – original draft, Writing – review & editing. Carlos Carpio: Data curation, Writing – original draft, Writing – review & editing, Software, Validation. Marta Moreno: Investigation. Ana Arancón: Investigation. Catalina Lara: Investigation. Ester Pérez: Investigation. Carlos Jimenez: Investigation. Estefan Zamarron: Investigation. Inmaculada Jiménez-Nacher: Investigation. Alicia Herrero: Supervision. Rodolfo Alvarez-Sala: Supervision.

Declaration of competing interest

The authors declare no conflict of interest in this article.

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