



ORIGINAL ARTICLE

Comparison of bronchodilator response between Dosivent[®] and Aerochamber Plus[®] Flow-Vu[®] chambers in patients with bronchial hyperreactivity

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ABSTRACT

Background: Aerochambers are used for the administration of inhaled drugs. Dosivent[®] is a previously unstudied chamber. This study aimed to validate the Dosivent[®] chamber against the widely used Aerochamber Plus[®] Flow-Vu[®].

Methods: We conducted a non-randomized, open-label, cross-over-controlled, and clinical trial (NCT05821868) in 50 patients with a known positive bronchodilator test. Bronchodilator washout was performed according to standard recommendations. Fifteen minutes after the administration of 400 µg of salbutamol with either chamber, the changes in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were measured. The agreement was measured by the intraclass correlation coefficient and Bland–Altman graphical analysis. Participants' satisfaction with the chamber was assessed with the FSI-10 questionnaire.

Results: The mean participant age was 58.0 (SD = 18.5) years, half were women, and only 31 (62%) participants had an FEV1/FVC of <0.7. The median increases in FEV1 obtained with the Aerochamber Plus[®] Flow-Vu[®] and Dosivent[®] were 0.28 L (interquartile range [IQR]: 0.21 – 0.38) and 0.29 L (IQR: 0.20 – 0.43), respectively, and the median increases in FVC were 0.29 L (IQR: 0.19 – 0.37) and 0.28 L (IQR: 0.19 – 0.45). The intraclass correlation coefficient for increases in FEV1 was 0.865, and it was 0.820 for increases in FVC. The median FSI-10 questionnaire score was 42 (IQR: 37 – 47) with Aerochamber Plus[®] Flow-Vu[®] and 44 (39 – 48) with Dosivent[®] ($P < 0.001$).

Conclusions: Our study revealed a strong agreement between salbutamol responses when utilizing both the Dosivent[®] and Aerochamber Plus[®] Flow-Vu[®] chambers. This suggests that these devices are interchangeable and can be effectively employed in routine clinical practice.

Relevance for Patients: For patients using inhaled medications, this study provides reassurance regarding the equivalence of the Dosivent[®] chamber with the widely used Aerochamber Plus[®] Flow-Vu[®]. This provides patients with more options for device selection, potentially improving convenience and satisfaction with their inhalation therapy. Patients and healthcare providers can consider the Dosivent[®] chamber as a viable alternative, which may positively impact treatment adherence and overall respiratory health management.

1. Introduction

Inhaled therapy is an airway administration route for bronchodilator and anti-inflammatory drugs that are widely used in patients with obstructive respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) [1,2]. It is also often used in pulmonary function laboratories for bronchodilator tests [3,4]. This method of administration allows a

direct deposit of drugs into the airway and, therefore, reduces the amount of medication needed, minimizing the systemic effect of the drugs [5].

Metered dose inhalers (MDIs) present some advantages compared with other devices: They require no threshold inspiratory flow to trigger the release of the active compound, and they are cheap [6-8]. However, their use requires dexterity to complete the required sequential steps to achieve a correct inhalation of the medication; in particular, they require coordination between the pulsation of the cartridge and the inhalation. Incorrect completion of one or more steps in using an MDI can substantially reduce the administered medication delivery and consequently its effectiveness and safety. Numerous studies have demonstrated that 50 – 100% of patients do not use their inhaler devices correctly [9]. To overcome this limitation, MDIs are frequently used with add-on devices referred to as inhalation chambers (“chambers,” in the context of inhalation devices) [10]. Chambers act as reservoirs and reduce the speed at which the aerosol enters the mouth. This makes using the inhaler easier and helps ensure that more of the medication reaches the lungs [11].

Performing spirometry before and after the inhalation of bronchodilators (bronchodilator response [BDR] testing) is in diagnosing asthma and COPD [12,13]. In most laboratories, the bronchodilator drug (usually salbutamol/albuterol) is administered through a chamber. The Dosivent® inhalation chamber is designed to optimize the delivery of inhaled bronchodilators and corticosteroids in the treatment of respiratory diseases.

This study was conducted to compare the efficacy, as measured by changes in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC), of salbutamol inhaled with the Dosivent® chamber versus the widely used Aerochamber Plus® Flow-Vu® in patients with a positive BDR, as Dosivent® is a previously unstudied chamber.

2. Materials and Methods

2.1. Design

We conducted a non-randomized, open-label, crossover-controlled, and clinical trial in 50 patients with a previous positive BDR. The protocol was approved by the Drug Research Ethics Committee of the Gregorio Marañón General University Hospital (code 03/2022) and registered with registration number NCT05821868. All participants provided written informed consent before any study procedure. During the study, the principles of the Declaration of Helsinki and the current standards of Good Clinical Practice were followed.

2.2. Study population

Patients over 18 years of age were included who attended our center for a bronchodilator test, gave a positive result in this test, and provided written informed consent for participation in this study. Patients were excluded if Grade A quality spirometry was not obtained according to the classification in current guidelines [13] and, in the opinion of the investigator, performing a bronchodilator test could pose a risk to the patient or interrupting

the usual bronchodilator treatment could worsen the underlying respiratory pathology.

2.3. Sample size calculation

To achieve a statistical power of 80% and a significance level of a two-tailed $P < 0.05$, 45 patients were necessary for the study to detect a 5% of difference. A loss of 10% was anticipated, rendering a sample of 50 participants.

2.4. Study interventions

Before the BDR test, participants were asked to interrupt their usual bronchodilator medication according to standard washout recommendations [13]. On the first visit, after checking that the patient had followed the washout instructions, baseline spirometry was performed [13]. This was followed by the inhalation of 400 µg of salbutamol MDI through the Aerochamber Plus® Flow-Vu® chamber. A postbronchodilator spirometry was performed 15 min later. Patients then completed the Feeling of Satisfaction with Inhaler (FSI-10) questionnaire, and washing-out instructions were given for the next visit. Two days later, a similar BDR test was performed, this time using the Dosivent® chamber.

The main outcomes were changed in FEV1 and FVC, measured as absolute value and percentage (i.e., [postbronchodilator FEV1 or FVC – prebronchodilator FEV1 or FVC]/prebronchodilator FEV1 or FVC).

The secondary outcome was the difference in FSI-10 score between the two chambers.

Other variables such as demographic data, underlying lung disease, and adverse effects were collected from medical records and the anamnesis on the day of the bronchodilator tests.

2.5. Statistical analysis

Quantitative variables are described as mean and standard deviation (SD) or should the normality assumption not hold, median, and interquartile range (IQR). The Friedman test was used for two-tailed statistical comparisons of between-groups changes in FEV1, FVC, and FSI-10 questionnaire score. To evaluate the agreement between BDR with both chambers, the intraclass correlation coefficient and Bland–Altman graphic analysis were performed. For the latter, the ordinates were the difference between the Dosivent® and Aerochamber Plus® Flow-Vu®. Statistical significance was established at $P < 0.05$ for all comparisons. Stata version 15 was used to generate the Bland–Altman plots. All other analyses were performed with SPSS version 26.

3. Results

Fifty-six patients were invited to participate in the study. Of these, 50 provided written informed consent and were included in the study. No participant dropped out of the study (Figure 1).

Twenty-five (50%) of the participants were men. The mean age was 58 (SD 18) years, the mean height was 1.64 m (0.1), the mean weight was 75.1 kg (17.5), and the mean body mass index

was 27.9 kg/m²(6.0). The mean prebronchodilator FEV1 and FVC were 2.11 L (0.83) and 3.15 L (0.97), respectively. Thirty-one participants (62%) had a prebronchodilator FEV1/FVC < 0.70. Regarding pulmonary disease, 14 participants (28%) had COPD, and 22 (44%) had bronchial asthma (Table 1).

The median increases in FEV1 obtained with the Aerochamber Plus® Flow-Vu® and Dosivent® were 0.28 L (IQR: 0.21 – 0.38) and 0.29 L (0.20 – 0.43), respectively; these differences were non-significant (Table 2). The median increases in FVC were 0.29 L (0.19 – 0.37) and 0.28 L (188 – 453), also non-significant (Table 3).

The agreement in BDR between the chambers was excellent, with intraclass correlation coefficients of 0.865 and 0.820, respectively, for FEV1 and FVC. Figures 2 and 3 show the Bland–Altman graph for the increases in FEV1 and FVC with both chambers. Regarding FEV1, 3 participants (6%) were outside the lower limit of agreement. For FVC, 3 participants (6%) were outside the limits of agreement: Two below the lower limit and one above the upper limit.

Participants’ satisfaction favored the Dosivent®, with a median FSI-10 score of 44 (IQR: 39 – 48) compared to 42 (IQR: 37 – 47) with the Aerochamber Plus® Flow-Vu®; this difference was statistically significant (*P* < 0.001). No adverse events were observed during the study.

4. Discussion

In our study, we observed a high level of concordance [14,15] in the BDR after the inhalation of 400 µg of salbutamol through both the Dosivent® and Aerochamber Plus® Flow-Vu® chambers.

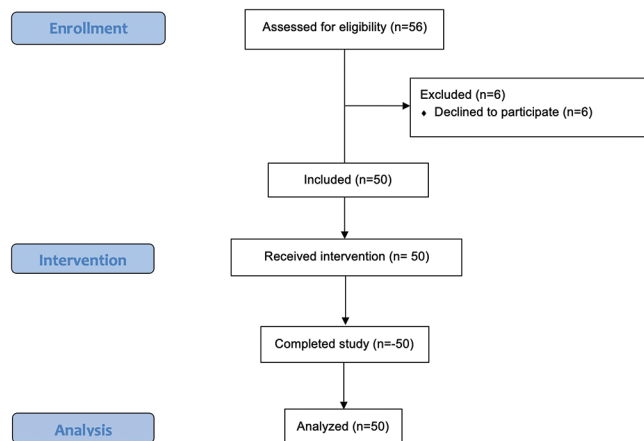


Figure 1. CONSORT diagram.

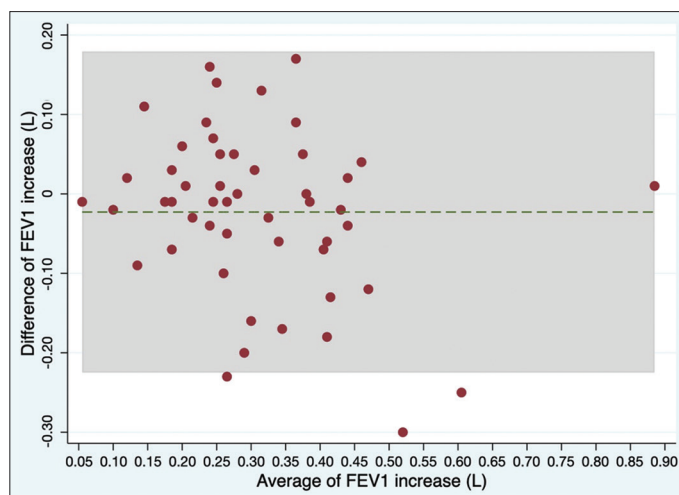


Figure 2. Bland-Altman plot representing concordance between forced respiratory volume during first second increase with Aerochamber Plus® Flow Vu® and Dosivent®.

Table 1. Subjects’ demographic and clinical characteristics

Characteristic	N or mean	% or SD
Male	25	50
Age	58.0 years	18.5
Height	164.0 cm	10.0
Weight	75.1 kg	17.5
BMI	27.9 kg/m ²	6.0
FEV1 prebronchodilator	2.11	0.83
FVC prebronchodilator	3.15	0.97
Obstruction prebronchodilator	31	62
COPD	14	28
Asthma	22	44

BMI: Body mass index; FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; COPD: Chronic obstructive pulmonary disease

Table 2. FEV1 and FEV1 increase comparison according to aerochamber

Median (IQR)	FEV1 pre-BD L	FEV1 post-BD L	FEV1 increase L	FEV1 increase %
Aerochamber®	1.97 (1.51 – 2.66)	2.27 (1.72 – 3.04)	0.28 (0.21 – 0.38)	13.4 (11.6 – 17.2)
Dosivent®	1.96 (1.51 – 2.66)	2.30 (1.75 – 3.02)	0.29 (0.20 – 0.43)	13.8 (12.1 – 17.3)
<i>P</i> -value	0.668	0.258	0.248	0.777

IQR: Interquartile range; FEV1: Forced respiratory volume during first second; BD: Bronchodilator.

Table 3. FVC and FVC increase comparison according to aerochamber

Median (IQR)	FVC pre-BD L	FVC post-BD L	FVC increase L	FVC increase %
Aerochamber®	3.10 (2.34 – 3.81)	3.43 (2.57 – 4.01)	0.29 (0.19 – 0.37)	10.6 (5.3 – 12.5)
Dosivent®	3.05 (2.35 – 3.83)	3.44 (2.56 – 4.07)	0.28 (0.19 – 0.45)	11.6 (5.9 – 14.1)
<i>P</i> -value	0.662	0.090	0.886	0.777

IQR: Interquartile range; FVC: Forced vital capacity; BD: Bronchodilator.

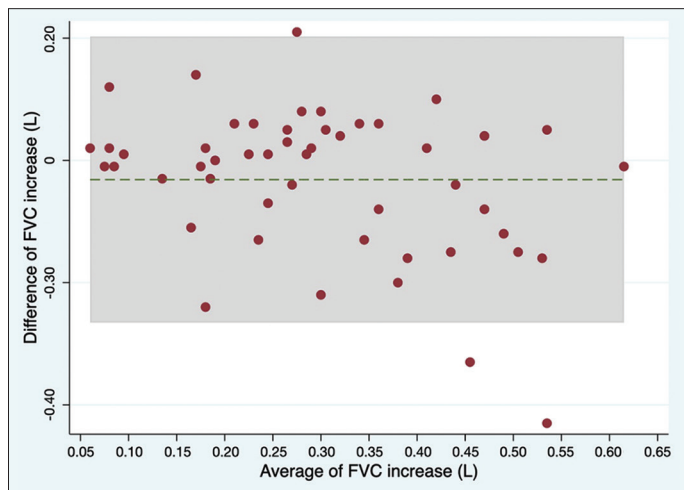


Figure 3. Bland-Altman plot representing concordance between forced vital capacity increase with Aerochamber Plus® Flow Vu® and Dosivent®.

In addition, we observed that the bronchial response to salbutamol was reproducible over a 2-day period.

In the literature, few comparative studies exist between different chambers, and no previous study has included Dosivent®. Most, like ours, have compared the increase in FEV1 after the administration of a bronchodilator through different devices [16-18]. Some have also compared the FEV1 change with different chambers and the direct administration of the MDI [16]. We used the Aerochamber Plus® Flow-Vu® for comparison because it is commonly used. It has also been widely studied in patients of different ages, with different respiratory diseases, and whose characteristics are well known both *in vitro* and *in vivo* with different inhalers [19-24]. We found excellent agreement according to the intraclass correlation coefficient. The Bland-Altman plot also showed good agreement, with only 6% of the point outside the 95% confidence interval.

We found no comparative study on the satisfaction of patients with different chambers. In our study, we found a slightly but significantly higher FSI-10 score with the Dosivent® relative to the Aerochamber Plus® Flow-Vu®. The FSI-10 questionnaire evaluates the subjective satisfaction of patients with inhalers and has been widely used for patients with different pulmonary pathologies [25-27]. It was not specifically designed to evaluate inhalation chambers, but its questions refer to the ease of use of the devices and chambers.

The main strength of our study is that we included patients with both known and newly diagnosed diseases, as well as patients of both sexes, with and without baseline airflow obstruction.

Our study also has limitations. First, since it was not randomized, it could have been influenced by the moment in which the tests were performed. However, only one patient had a negative BDR (different with each chamber), the washout procedure was similar for the two tests, and the sessions were separated only by 2 days. Second, the sample size did not allow sufficient statistical power to analyze the subgroups of participants. Third, we have only analyzed the change in FEV1 with the administration of salbutamol

400 µg. Other doses of salbutamol and other bronchodilators should be studied in future studies.

This study may impact clinical practice since the previously non-validated Dosivent® chamber showed similar performance to another commonly used inhalation chamber, and it seems more satisfactory for users.

5. Conclusions

The Dosivent® chamber demonstrated excellent agreement with the Aerochamber Plus® Flow-Vu® in terms of the increase in FEV1 and FVC during a bronchodilator test. Therefore, in routine clinical practice, it is viable to use both chambers interchangeably contingent on the preferences of the patient and professional.

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Conflicts of Interest

L.P.-M. has received funding from GSK, Chiesi, and Sanofi and has received consulting fees from MSK. All other authors have no conflicts of interest to declare.

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