Comparative Effect of Beclomethasone Dipropionate and Cetirizine on Acoustic Rhinometry Parameters in Children With Perennial Allergic Rhinitis: A Randomized Controlled Trial

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Abstract

Background: The effect of intranasal corticosteroids and oral antihistamines on acoustic rhinometry parameters has not been directly compared. Objectives: The primary objective was to compare the effect of a 21-day course of treatment with nasal beclomethasone dipropionate (nBDP) with that of cetirizine (CTZ) on nasal patency measured using acoustic rhinometry in children with perennial allergic rhinitis (PAR). The secondary objective was to compare the effect of both drugs on nasal cytology, symptom severity, sleep quality, and quality of life. Methods: In this 21-day, open-label, randomized controlled study, 34 children with PAR (age 6-14 years) with a Total 5-Symptom Score (T5SS) ≥5 received nBDP 100 µg per nostril twice daily or CTZ 10 mg tablets once daily. The measures of effect were the least square mean change (LSmc) in nasal volume, minimal cross-sectional area (MCA), and nasal cytology, as well as the scores on the T5SS, Pittsburgh Sleep Quality Index (PSQI), and Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). Results: After 21 days, nBDP improved nasal volume and MCA more than CTZ (LSmc, 2.21 cm³ vs 0.20 cm³ [P=.013]; and LSmc 0.63 cm² vs 0.13 cm² [P=0.02], respectively). Compared with the CTZ group, a more marked improvement was found in the nBDP group with respect to eosinophil classes (LSmc, −1.10 vs −0.40; P=0.031) and neutrophil classes (LSmc, −0.97 vs −0.17; P=0.010), T5SS (LSmc, −5.63 vs −3.54; P=0.008), PSQI (LSmc, −1.30 vs −0.19; P=0.025), and PRQLQ total scores (LSmc, −1.15 vs −0.69; P=0.031).

Conclusions: In children with PAR, nBDP is more effective than CTZ in improving nasal patency measured by acoustic rhinometry, with associated beneficial effects on nasal cytology, symptoms, sleep quality, and quality of life.

Key words: Acoustic rhinometry. Allergic rhinitis. Beclomethasone dipropionate. Cetirizine. Children. Nasal patency.
Introduction

Allergic rhinitis is the most common form of rhinitis in childhood. It is characterized by at least 2 symptoms from among nasal itching, sneezing, rhinorrhea, and nasal congestion [1]. In particular, nasal congestion, defined as the discomfort experienced during breathing due to decreased nasal patency, is recognized as one of the most bothersome symptoms [2,3].

Nasal patency can be evaluated subjectively using symptom severity scales [4-6] or objectively using clinical measures [7], such as acoustic rhinometry, a validated noninvasive tool applied to measure the area and volume of the nasal cavity [8]. In children, measurement of volume in the anterior part of the nose has been shown to be sensitive for changes in nasal patency due to changes in mucosal swelling after the nasal provocation test [9] and after decongestion [10]. Nasal cytology can also be used for objective evaluation of mucosal inflammation and provides insights into the efficacy of therapeutic interventions [11,12].

There is strong evidence for the efficacy of intranasal corticosteroids (INCs) in patients with perennial allergic rhinitis (PAR) [13]. Nasal beclomethasone dipropionate (nBDP), in particular, has been shown to be effective both in reducing eosinophils and lymphocytes in the nasal mucosa and in relieving nasal symptoms [14]. Oral antihistamines are also recommended [13], and cetirizine (CTZ) has proven effective in relieving symptoms [15].

Previous clinical studies in children with PAR demonstrated the efficacy of INCs and oral antihistamines in improving acoustic rhinometry parameters and other objective outcomes [16,17]. However, these outcomes were evaluated only through independent intragroup analyses or comparisons with placebo, and no studies directly compared both active treatments. Moreover, previous studies used different methodologies and therapeutic interventions, with the result that objective and subjective outcomes have not been comprehensively evaluated.

The primary aim of the present study was to compare the effect of nBDP with that of CTZ on nasal patency measured using acoustic rhinometry in children with PAR. The secondary aim was to compare the effect of nBDP and CTZ on other objective parameters (nasal cytology) and subjective parameters (nasal symptom severity, sleep quality, quality of life).

Materials and Methods

Study Design

This single-center, open-label, randomized controlled study was approved by the local Institutional Ethics Committee (Palermo 1, Italy, Approval Number: 09/2015), and informed consent was obtained from all parents before study entry. Once approved, the study was registered on ClinicalTrials.gov (ID: NCT02646904). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Participants

The initial study population comprised 128 children with PAR. The children were aged 6-14 years and had been assessed for eligibility at the pediatric allergy outpatient clinic of the Institute of Biomedicine and Molecular Immunology, National Research Council of Italy, Palermo, Italy between May 2016 and July 2017. The inclusion criteria were as follows: (1) age 6-14 years; (2) clinical history of PAR in the previous year, according to ARIA guidelines [18]; (3) allergic sensitization to Dermatophagoides pteronyssinus, defined as a positive skin prick test response (wheal ≥3 mm larger than the negative control test [Stallergenes]) after 15 minutes [19]; (4) Total 5-Symptom Score (T5SS) ≥5 (rhinorrhea, nasal obstruction, nasal itching, sneezing, eye itching) [4] in the previous week. The exclusion criteria were as follows: (1) positive skin prick test result to seasonal allergens and other perennial allergens; (2) medical diagnosis of nasal anatomic defects (ie, deviated septum) or nasal polydrip disease; (3) medical diagnosis of asthma according to GINA guidelines (http://ginasthma.org); (4) upper or lower respiratory tract infection in the previous 2 weeks; (5) use of oral antihistamines, decongestants, leukotriene antagonists, systemic/topical antibiotics or corticosteroids in the previous 4 weeks; (6) ongoing allergen immunotherapy; (7) active smoking; (8) adherence <80%.

Interventions

According to a computer-generated randomization sequence (1:1 allocation) that was unknown to the physicians, the 68 eligible patients were assigned to one of two 21-day treatments: 34 children received nBDP 100 μg per nostril twice daily (beclomethasone dipropionate nasal spray suspension); 34 children received CTZ 10 mg once daily (oral tablets, 10 mg). Both nBDP and CTZ were provided by CHIESI Farmaceutici S.p.A. All patients and their caregivers were given a brief demonstration of how to use the nasal spray suspension.

Outcomes

The primary outcome was the change from baseline to 21 days of treatment in acoustic rhinometry parameters, namely, nasal volume and minimal cross-sectional area (MCA). Acoustic rhinometry was carried out using the A1 Acoustic Rhinometer (GM Instruments) and the accompanying software according to the manufacturer’s instructions. All measurements

Conclusions: en niños con PAR, la nBDP es más efectiva que la CTZ en mejorar la obstrucción nasal medida por rinometría acústica, con los beneficios asociados sobre citología nasal, síntomas, calidad de sueño y calidad de vida.

Key words: Rinometría acústica. Rinitis alérgica. Dipropionato de beclometasona. Ceterizina. Niños. Obstrucción nasal.
were performed by the same pediatrician (VM). The device
was calibrated prior to each measurement. Following current
recommendations, patients were tested after 20 minutes of
acclimatization in the test room [20]. Special soft nosepieces
for children were used. If necessary, ultrasound gel was used
to prevent acoustic leakage. No nasal decongestant was used.
Calculations were based on the mean values of 3 acceptable
measurements with a standard deviation of less than 5%. The
values of special interest were the nasal volume (cm$^3$) in the
first 5 cm from the nostril and the MCA (cm$^3$). Total values
were calculated by adding each nostril value.

The secondary outcomes were the changes from baseline
to 21 days of treatment in nasal cytology classes and in a series
of subjective scales (see below).

Nasal cytology was performed using a small plastic
curette (Rhinoprobe) in anterior rhinoscopy, following recent
recommendations [21]. Neutrophils and eosinophils were
classified as follows: 0, none; 1, few scattered cells; 2, moderate
number; 3, large clusters [21].

The T5SS is a subjective scoring system for determination
of symptom severity based on 5 domains: rhinorrhea, nasal
obstruction, nasal itching, sneezing, and eye itching. Each
symptom is scored on a 4-point scale from 0 to 3. The total
score is calculated by adding the scores for all 5 domains and
ranges from 0 (nonsevere) to 15 (extremely severe) [4].

The Pittsburgh Sleep Quality Index (PSQI) is a self-
administered questionnaire based on 4-week recall and
including 19 questions in 7 domains: subjective sleep quality,
sleep latency, sleep duration, habitual sleep efficiency,
sleep disturbance, use of sleep medications, and daytime
dysfunction. Each domain is scored from 0 to 3, so that the total
score ranges from 0 (good sleeper) to 21 (poor sleeper) [22].

The Paediatric Rhinoconjunctivitis Quality of Life
Questionnaire (PRQLQ) is a self-administered questionnaire
based on 4-week recall for assessing physical, emotional,
and social problems in persons with allergic rhinitis. It includes 23
items in 5 domains: nose symptoms, eye symptoms, practical
problems, activity limitation, and other symptoms. Each
domain is scored on a 7-point scale (from 0 [good quality] to
6 [poor quality]). The overall score is obtained from the mean
score of all the items [23].

**Assessments**

A detailed medical history was obtained by well-trained
physicians (VM, GF, SLG) to investigate clinical symptoms,
host factors, and environmental exposures. In particular,
information about current exposure (previous 12 months) to
passive smoke, mold, pet dander, and traffic was derived from
a standardized questionnaire administered to parents [24].

The study involved 3 visits: screening (visit 1), randomization
(visit 2, baseline), and final assessment (visit 3, day 21+1). At
visit 1, patients were assessed for eligibility and recruited if
they met the inclusion criteria. Typically, 1 to 7 days elapsed
from enrolment to randomization. Patients underwent a physical
examination, and study variables were assessed at each visit.
When necessary, questionnaires were completed under the
supervision of one of the researchers (LM) during the visits.

Patients and caregivers were instructed to record the
occurrence and severity of adverse effects on a diary

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**Figure 1.** Study flowchart. ITT indicates intention-to-treat; CTZ, cetirizine; nBDP, nasal beclomethasone dipropionate.

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**Sample Size**

The sample size was based on pilot data from a previous
study [17] investigating the effect of topical nasal corticosteroids
on nasal volume in children and adolescents with PAR. In the
aforementioned study, the nasal volume increased from a
baseline mean value of 8.2 cm$^3$ to 9.3 cm$^3$ (SD approximately
1.5). Detecting a similar change with an 80% statistical power
and a 5% significance level would have required a sample
size of 30 children for each treatment group. To account for
a hypothesized dropout rate of 10% to 15%, the sample size
was established at 34 patients per group.

**Statistical Analysis**

The baseline characteristics of the children were compared
between the nBDP and CTZ groups using the $t$ test for
2 means (quantitative variables) and the $\chi^2$ test for percentages
(categorical variables). Correlations between acoustic
rhinometry parameters and other objective and subjective
scores were evaluated using the Kendall $\tau$ test.

The treatment effect was assessed in children who
completed the study. For the primary outcomes, an exploratory
analysis was performed using the Wilcoxon test to assess the
change from baseline in the 2 treatment groups. For both the
primary and secondary outcome measures, the mean change
from baseline in the 2 treatment groups was compared using
linear regression models adjusted for age, weight, current
exposure to smoke, mold, dander (cat and/or dog), traffic

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**Table:**

| Assessed for eligibility | (N=128) |
|-------------------------|---------|
| Excluded (n=60)         |
| (violation of entry criteria or detection of exclusion criteria) |
| Randomized              |
| (ITT population: n=68) |
| CTZ                     |
| (n=34)                 |
| nBDP                    |
| (n=34)                 |
| Dropouts (n=3) 1 consent withdrawal 2 lost to follow-up |
| No dropouts            |
| Completed (n=31)       |
| Completed (n=34)       |
Table 1. Characteristics of Children at Baseline

|                      | CTZ (n=34) | nBDP (n=34) | P Value |
|----------------------|------------|-------------|---------|
| **Anthropometric characteristics** |            |             |         |
| Gender               |            |             | .800    |
| Male                 | 23 (68%)   | 21 (62%)    |         |
| Female               | 11 (32%)   | 13 (38%)    |         |
| Mean (SD) age, y     | 9.47 (2.36)| 10.06 (2.35)| .307    |
| Mean (SD) weight, kg | 36.94 (11.2)| 37.56 (14.0)| .842    |
| Mean (SD) height, cm | 139 (14.47)| 139.59 (16.37)| .877   |
| **AR duration, y**   |            |             | .487    |
| 1-3                  | 16 (47%)   | 14 (41%)    |         |
| 4-5                  | 5 (15%)    | 9 (28%)     |         |
| >5                   | 13 (38%)   | 11 (31%)    |         |
| **Current environmental exposures<sup>a</sup>** |            |             |         |
| Passive smoke        | 8 (24%)    | 8 (24%)     | 1.000   |
| Mold                 | 8 (24%)    | 5 (15%)     | .537    |
| Dog                  | 9 (26%)    | 6 (18%)     | .559    |
| Cat                  | 3 (9%)     | 3 (9%)      | 1.000   |
| **Traffic density**  |            |             | .576    |
| Absent               | 4 (12%)    | 6 (18%)     |         |
| Low                  | 10 (29%)   | 13 (38%)    |         |
| Moderate             | 7 (21%)    | 7 (21%)     |         |
| High                 | 13 (38%)   | 8 (24%)     |         |

Abbreviations: AR, allergic rhinitis; CTZ, cetirizine; nBDP, nasal beclomethasone dipropionate.
<sup>a</sup>t test for quantitative variables, χ² test for categorical variables.
<sup>b</sup>Previous 12 months.

Results

Descriptive Statistics

Of the 128 screened patients, 60 were excluded owing to violation of the entry criteria or detection of exclusion criteria (Figure 1). Overall, 65 of the 68 randomized children (96%) completed the study. In particular, of the 34 patients randomized to CTZ, 31 completed the study: 1 patient (3%) withdrew consent, and 2 children (6%) were lost to follow-up (change of residence). All the 34 patients randomized to nBDP completed the study. Demographic characteristics and current environmental exposures (previous 12 months) were similar between the 2 groups at baseline (Table 1). Baseline values of the primary and secondary outcomes were also comparable (Table 2).

Eosinophil classes were negatively correlated with volume (Kendall τ, –0.21; P = .003) and MCA (Kendall τ, –0.14; P = .040) for both groups at both visits (Figure 2), while correlations between acoustic rhinometry parameters and all the subjective scores were not statistically significant.

For children who completed the study, the level of adherence was 100% in both treatment groups, no adverse events were observed, and no concomitant medication use was reported.

Primary Outcome

The exploratory analysis showed that volume values increased significantly after 21 days in the nBDP group (P = .033), while the change was not significant in the CTZ group (P = .900) (Figure 3, top panels). Similarly, MCA values increased significantly in the nBDP group (P = .045), while the change was not significant in the CTZ group (P = .840) (Figure 3, bottom panels). After adjusting for confounders, nBDP was found to improve nasal volume more than CTZ (LSmc, 2.21 cm³ vs 0.20 cm³; P = .013) (Table 3). Similarly, nBDP improved MCA more than CTZ (LSmc, 0.63 cm² vs 0.13 cm²; P = .002).

Table 2. Primary and Secondary Outcomes at Baseline

|                      | CTZ (n=34) | nBDP (n=34) | P Value |
|----------------------|------------|-------------|---------|
| **Acoustic rhinometry** |            |             |         |
| Volume, cm³          | 5.77 (1.51)| 5.91 (1.49)| .703    |
| MCA, cm²             | 0.68 (0.32)| 0.69 (0.25)| .893    |
| **Nasal cytology**   |            |             |         |
| Eosinophil classes   |            |             | .255    |
| None (score=0)       | 10 (31%)   | 16 (50%)    |         |
| Few scattered cells  | 8 (25%)    | 5 (16%)     |         |
| Moderate number (score=2) | 12 (38%) | 7 (22%)     |         |
| Large clusters (score=3) | 2 (6%)    | 4 (12%)     |         |
| Neutrophil classes   |            |             | .223    |
| None (score=0)       | 15 (47%)   | 21 (66%)    |         |
| Few scattered cells  | 2 (6%)     | 2 (6%)      |         |
| Moderate number (score=2) | 4 (12%)  | 5 (16%)     |         |
| Large clusters (score=3) | 11 (34%) | 4 (12%)     |         |
| TSSS total score     | 8.56 (2.7) | 8.21 (2.56)| .591    |
| PSQI total score     | 7.28 (1.89)| 6.79 (3.13)| .446    |
| PRQLQ total score    | 3 (1.21)   | 2.74 (1.13)| .383    |

Abbreviations: CTZ, cetirizine; nBDP, nasal beclomethasone dipropionate; MCA, minimal cross-sectional area; PRQLQ, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; PSQI, Pittsburgh Sleep Quality Index; TSSS, Total 5-Symptom Score.
<sup>a</sup>Data are presented as mean (SD) for quantitative variables, No. (%) for categorical variables.
<sup>b</sup>t test for quantitative variables; χ² test for categorical variables.
Secondary Outcomes

In the nBDP group, with respect to the CTZ group, a more pronounced improvement was observed in eosinophil classes (LSmc, –1.10 vs –0.40, P=.031) and neutrophil classes (LSmc, –0.97 vs –0.17, P=.010), T5SS total score (LSmc, –5.63 vs –3.54, P=.008), PSQI total score (LSmc, –1.30 vs –0.19, P=.025), and PRQLQ total score (LSmc, –1.15 vs –0.69, P=.031) (Table 3).

Discussion

The present study demonstrates that a 21-day course of treatment with nBDP is more effective than oral CTZ for improving nasal patency as measured using acoustic rhinometry in children with PAR.

Despite its feasibility and noninvasiveness, acoustic rhinometry is not extensively used in children, probably because of the weak correlation with self-reported nasal congestion [25,26], which was also shown in the present study. The very few studies that have evaluated acoustic rhinometry for assessment of PAR in children are characterized by differences in the study design and the INCs administered [16,17,27]. Since none of these studies evaluated the effect of nBDP, the findings of the present study can be only partially compared with previous results.

We observed significant improvements in nasal volume in the first 5 cm from the nostril and in MCA, thus indicating the anti-inflammatory effect of nBDP. The reported effects were expressed in terms of LSmc, which represents the predicted means of the outcomes in a hypothetical population of patients with a balanced (uniform) distribution of the variables included in the model, specifically, age, weight, current exposure to smoke, mold, dog/cat dander, traffic density, and baseline value of the variable of interest. As a result, LSmc is expressed in the same unit of measurement as the outcomes and, therefore, has real, direct clinical significance. As highlighted by Straszek et al [10], the sensitivity of volume parameters to changes in nasal patency has to be ascribed to the change in mucosal swelling. However, previous studies reported somewhat discordant findings. In particular, a similar result was observed by Wandalsen et al [17], where the authors evaluated the effect of a 21-day course of once-daily mometasone furoate 100 µg and found a significant increase in all of the acoustic rhinometry parameters investigated, as well as a decrease in the nasal symptom score. In contrast, a similar result was observed by Wandalsen et al [17], where the authors evaluated the effect of a 21-day course of once-daily mometasone furoate 100 µg and found a significant increase in all of the acoustic rhinometry parameters investigated, as well as a decrease in the nasal symptom score. In contrast, de Andrade et al [27] did not observe significant differences in nasal cavity volume after a 6-week course of fluticasone propionate.

nBDP was also found to improve nasal volume and MCA to a greater extent than CTZ. Even though INCs and antihistamines have been assessed in placebo-controlled trials in children with PAR [16,28], their effect on nasal patency has not been explicitly compared. In the present study, the greater effect of nBDP in comparison with CTZ was also corroborated by the higher reduction in counts of nasal inflammatory cells, such as eosinophils and neutrophils. This reinforces the results of a placebo-controlled study [29], which did not include an antihistamine arm, thus providing more evidence of the efficacy of nBDP in decreasing the chronic inflammation of the upper airways in patients monosensitized to the perennial allergen D pteronyssinus.

The current study also integrates previous findings about the efficacy of nBDP in improving symptom severity in children [30] and adolescents [31] with PAR, as well as its effect on quality of life [31] and sleep quality [32,33]. Specifically, nBDP was found to improve the T5SS, PSQI, and PRQLQ scores more than CTZ. Of note, none of the available
studies investigating the effect of different treatments on nasal patency used a comprehensive approach including subjective outcomes such as sleep quality and quality of life [16,17,27]. The importance of assessing these parameters in clinical practice has been emphasized as part of a holistic approach that can also be adopted when treating children. In fact, it is well known that the symptoms of PAR can negatively affect children’s activities and sleep quality, leading to daytime somnolence and fatigue [34].

The main novelty of our study is the comparative investigation of the effect of topical nBDP and oral CTZ on nasal patency in children with PAR measured using acoustic rhinometry and other objective and subjective outcomes. In fact, the more pronounced effect of nBDP in comparison with CTZ was supported by concomitant improvements in nasal cytology and in scores for nasal symptom severity, quality of life, and sleep quality. Such comprehensive assessment may prove useful in the clinical management of children with PAR.

Even if 3 patients dropped out of the CTZ group (31 completed the study), this did not affect the desired power of the study, since 30 patients per group would have been enough (see Sample Size). Another positive aspect is...
the very good adherence to daily treatment (100% in both groups), thanks to close telephone follow-up by well-trained investigators. nBDP treatment was also well tolerated, and no adverse events were observed.

The main limitation of the present study is the fact that patients and investigators were not blinded to treatment. However, this may not have affected the results owing to the objective nature of the primary outcomes (and concordant results found for the secondary outcomes). Our study is also limited by the absence of an objective evaluation of drug safety. We did not perform such an evaluation in the light of the results of a recent study on nasal treatment with nBDP, which failed to show a significant systemic effect in treated children with PAR [35]. The lack of hypothalamus-pituitary-adrenal axis suppression may be attributable to the low systemic bioavailability of nBDP resulting from low absorption through respiratory and digestive mucus membranes [36].

Conclusions

The current study demonstrated the greater effect of nBDP in comparison with CTZ on nasal permeability measured using acoustic rhinometry in children with PAR. Similarly, a greater anti-inflammatory effect of nBDP resulted in reduced nasal inflammatory cell counts. Moreover, nBDP proved to be effective in reducing the subjective burden perceived by patients, with beneficial effects on symptom severity, quality of life, and sleep quality.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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