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Balancing control and safety: hypothalamic-pituitary-adrenal axis effects of dual-route fluticasone in unified airway disease

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Abstract

The concurrent presence of allergic rhinitis and bronchial asthma, known as unified airway disease, often requires combined therapeutic approaches. This prospective study investigates the clinical efficacy and safety of combined inhaled and intranasal fluticasone propionate in such patients. A total of 25 adult patients with moderate to severe allergic rhinitis and bronchial asthma were enrolled. After excluding 2 lost-to-follow-up patients, 23 patients completed the study. Participants received combined inhaled and intranasal fluticasone propionate for four weeks. Clinical outcomes were assessed using Total Nasal Symptom Score (TNSS), Asthma Control Test (ACT), spirometry, and 24-hour urinary free cortisol levels pre- and post-treatment. Significant improvements were observed in TNSS (9.09±2.89 to 2.13±1.62; $p<0.0001$) and ACT scores (20.48±3.07 to 24.09±1.12; $p<0.0001$). Pulmonary function tests showed significant increases in forced vital capacity from 3.16±0.73 L to 3.75±0.63 L ($p=0.0053$) and forced expiratory volume in 1 second from 2.18±0.75 L to 2.71±0.80 L ($p=0.0252$). Mean urinary free cortisol levels decreased from 31.35±9.35 mcg/24 h to 28.02±9.14 mcg/24 h, though the change was not statistically significant ($p=0.2295$). Combined inhaled and intranasal fluticasone propionate therapy significantly improves symptom control and pulmonary function in patients with allergic rhinitis and bronchial asthma. No significant suppression of the hypothalamic-pituitary-adrenal axis was observed, indicating a favorable safety profile for short-term use.

Key words: allergic rhinitis, bronchial asthma, inhaled corticosteroids, hypothalamic-pituitary-adrenal axis, unified airway disease.

Introduction

Allergic rhinitis and bronchial asthma are chronic inflammatory conditions that frequently coexist. Combined Allergic Rhinitis and Asthma Syndrome (CARAS) is characterized by inflammation of the upper and lower respiratory tracts and is also referred to as Unified Airway Disease as they both share the common patho-physiological mechanism [1]. Respiratory allergies pose a significant burden to the world economy. World health organisation estimated that around 15 million disability-adjusted life years (DALYs) are annually lost globally credited to bronchial asthma [2]. The Global Initiative for Asthma (GINA) estimates that around 300 million people around the world are suffering from bronchial asthma and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines state that about 10%-40% of world population is affected by allergic rhinitis. Around 40% of patients of allergic rhinitis also have bronchial asthma and about 80% asthma patients experience allergic rhinitis symptoms [3]. Both these guidelines advocate an integrated approach for managing the patients having CARAS [4,5]. Corticosteroids are the mainstay for managing the two allergic conditions as they improve symptom control and reduce exacerbations.

Fluticasone propionate, a synthetic corticosteroid with potent anti-inflammatory properties, is extensively prescribed via inhaled and intranasal routes for the treatment of asthma and allergic rhinitis, respectively. Its widespread use is attributed to its favourable pharmacokinetic profile, including high glucocorticoid receptor affinity and extensive first-pass metabolism, which theoretically limits systemic effects [6,7]. However, emerging evidence suggests that even topically administered corticosteroids can be absorbed into the systemic circulation, potentially impacting the hypothalamic-pituitary-adrenal (HPA) axis [8]. The HPA axis is a critical neuro-endocrine system responsible for the regulation of endogenous cortisol production in response to stress and metabolic needs. Exogenous corticosteroids, even when administered through inhaled or intranasal routes, can suppress this axis, leading to reduced cortisol biosynthesis and, in severe cases, secondary adrenal insufficiency [9]. Suppression of the HPA axis is of particular concern in patients receiving combined (from two routes) or high-dose corticosteroid therapy, as cumulative exposure may increase systemic bioavailability [10]. Clinical manifestations of adrenal suppression are often subtle but may include fatigue, hypotension, hyponatremia, and in extreme situations, may cause adrenal crisis—a potentially life-threatening condition [11].

Although the individual effects of inhaled or intranasal corticosteroids on adrenal function have been extensively studied, limited data exist on the cumulative effect of concurrent use of both intranasal and inhaled preparations in patients with overlapping asthma and allergic

rhinitis. Moreover, no such study has been done on Indian population so far. This pilot study aimed to evaluate the impact of high dose combined inhaled and intranasal fluticasone propionate therapy on HPA axis function, in CARAS patients, with its clinical relevance and recommendations for safe practice.

Materials and Methods

This prospective, single-arm, open-label pilot study was conducted at our centre. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants.

Eligible participants were adults aged 18–60 years with a clinical diagnosis of both bronchial asthma and allergic rhinitis, as per the GINA 2023 guidelines [4] and the ARIA guidelines-2016 revision [5], respectively. Patients having mild to moderate, stable, persistent asthma and perennial allergic rhinitis, who were able to use the device correctly, were selected for the study. Important exclusion criteria were: persons having history of adrenal disorders or chronic systemic debilitating disease, pregnancy or lactation, exacerbations during the study, systemic corticosteroid use (Intramuscular, Intravenous or Oral) in the previous six weeks, use of medications affecting cortisol metabolism (e.g., oral contraceptive pills, ketoconazole, phenytoin, carbamazepine, phenobarbital, and rifampin), smokers, poor compliance, and those who had respiratory tract infections at or six weeks prior to the start of study.

All participants received a regimen of high dose inhaled fluticasone propionate at 1000 µg/day via metered-dose inhaler using spacer (as per the GINA classification of dose of inhaled corticosteroids) along with intranasal fluticasone propionate via nasal spray at 200 µg/day divided in two doses, as standard of care. The treatment duration was four weeks. Patients were instructed on proper inhaler and nasal spray techniques to ensure optimal drug delivery and adherence.

Outcome measures

Clinical, pulmonary, and biochemical parameters were assessed at baseline and at the end of 4 weeks.

1. Clinical parameters included two symptom scores:
    - Total Nasal Symptom Score (TNSS): A composite score evaluating nasal congestion, rhinorrhea, sneezing, and nasal itching. Each symptom was graded on a 0–3 scale, with a maximum score of 12.
    - Asthma Control Test (ACT): A validated 5-item questionnaire assessing asthma control, scored from 5 (poor control) to 25 (complete control).

2. Pulmonary function test was performed by flow spirometry using a calibrated spirometer (Helios 401 model, RMS, India) in accordance with ATS/ERS guidelines. Forced Vital Capacity (FVC) in litres (L) and Forced Expiratory Volume in 1 Second (FEV_1) in litres (L) were recorded.

3. Hypothalamic-Pituitary-Adrenal Axis Function was assessed by measuring 24-hour Urinary Free Cortisol (UFC) levels. UFC was measured using standard chemiluminescent immunoassay.

Data were analyzed using SPSS version 29.0.1 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Paired t-tests were used to compare pre- and post-treatment values. A p-value <0.05 was considered statistically significant.

Results

A total of 25 patients who met the inclusion and exclusion criteria were enrolled in the study. The cohort included 13 female patients with a mean age of 40.76 years and 10 male patients with a mean age of 46.5 years. Two participants were lost to follow-up, as they didn't turn up at the end of 4 weeks of treatment, thus 23 patients completed the study and were included in the final analysis. The effects of combined inhaled and intranasal fluticasone propionate therapy on clinical, functional, and biochemical parameters are summarized in Table 1.

At baseline, all patients underwent assessment with the Total Nasal Symptom Score and the Asthma Control Test. The average TNSS was 9.09 ± 2.89, indicating severe nasal symptoms, while the average ACT score was 20.48 ± 3.07, suggestive of suboptimal asthma control. Spirometric evaluation showed a mean Forced Vital Capacity (FVC) of 3.16 ± 0.73 L and Forced Expiratory Volume in one second (FEV_1) of 2.18 ± 0.75 L. Baseline mean 24-hour urinary free cortisol (UFC) was 31.35 ± 9.35 mcg/24 h.

Following four weeks of combined treatment with inhaled and intranasal fluticasone propionate, there was statistically significant clinical improvement both subjectively and objectively. TNSS was reduced to 2.13 ± 1.62 ($p < 0.0001$) indicating marked subjective improvement in rhinitis symptoms (Figure 1), and ACT scores improved to 24.09 ± 1.12 ($p < 0.0001$) which also shows that there was good subjective feeling of wellbeing and relief from symptoms due to asthma at the end of study period (Figure 2). Pulmonary function also improved significantly, with mean FVC increasing to 3.75 ± 0.63 L ($p = 0.0053$) and FEV_1 to 2.71 ± 0.80 L ($p = 0.0252$), giving objective improvement in asthma control (Figure 3). These

figures reflect a good upper and lower respiratory airway symptom control when treatment was given by both the routes simultaneously, even for a small 4-week period.

The mean post-treatment UFC level decreased to 28.02 ± 9.14 mcg/24 h, but the change was not statistically significant ($p = 0.2295$), indicating no significant suppression of the hypothalamic-pituitary-adrenal (HPA) axis on concomitant corticosteroid treatment by both the routes.

Clinically, only 2 of the 23 patients reported mild fatigue and lethargy, which were self-limiting and not associated with other signs or symptoms of adrenal suppression and did not require treatment interruption. The remaining 21 patients reported no adverse effects or clinical signs suggestive of HPA axis dysfunction.

Discussion

The study evaluated the effect of combined inhaled and intranasal fluticasone propionate therapy on hypothalamic-pituitary-adrenal (HPA) axis function and clinical outcomes in patients with coexisting bronchial asthma and allergic rhinitis. Over a 4-week period, significant improvements were observed in symptom control and pulmonary function, while no statistically significant suppression of adrenal function was detected, suggesting that this therapeutic approach is both effective and safe in the studied population.

The observed reduction in TNSS and improvement in Asthma Control Test scores reflect the clinical efficacy of fluticasone propionate in managing upper and lower airway inflammation. TNSS decreased by approximately 76%, indicating substantial relief from allergic rhinitis symptoms, while ACT scores increased by nearly 18%, suggesting improved asthma control. These results are consistent with prior studies that have demonstrated the efficacy of intranasal and inhaled corticosteroids in managing unified airway disease through local anti-inflammatory effects and restoration of mucosal function. Rafael Stelmach *et al* observed in their study that when patients with coexisting allergic rhinitis and bronchial asthma are treated with both intranasal and inhaled corticosteroids, they show an improved nasal and pulmonary symptom control, starting after 4 weeks of treatment and observed that failure to treat rhinitis in patients of unified airway disease might impair clinical control of asthma [12]. Erkka Valovirta had also advocated that combined treatment strategy for both rhinitis and asthma leads to a superior control of upper and lower airway symptoms [3].

Improvements in objective pulmonary function parameters further corroborated the clinical findings. Both FVC and FEV_1 showed statistically significant improvement, suggesting enhanced airway patency and improved ventilatory capacity following treatment. This aligns with the known benefits of inhaled corticosteroids in reducing bronchial inflammation and

airway hyperresponsiveness in asthma as highlighted by Peter J Barnes in his review article [13]. Moghaddam KG *et al* also demonstrated significant improvement in FVC and FEV_1 after 3 weeks of treatment with fluticasone propionate [14].

Importantly, while corticosteroids are effective anti-inflammatory agents, their systemic absorption—even when administered topically—can suppress the HPA axis. In our study, the 24-hour urinary free cortisol (UFC) levels showed a small, non-significant decline ($p = 0.2295$). This suggests that the combined use of intranasal and inhaled fluticasone propionate even at high doses does not result in clinically meaningful adrenal suppression over a 4-week period. These findings are in line with previous studies demonstrating that the systemic bioavailability of fluticasone propionate is low due to extensive first-pass metabolism and poor gastrointestinal absorption. Moghaddam KG *et al* found no significant suppression of HPA axis after inhaled high dose fluticasone propionate and beclomethasone dipropionate use for 3 weeks [14]. H Derendorf *et al* have showed in their review article that inhaled fluticasone has minimal chance of systemic effects [15]. Attilio L. Boner had concluded that intranasal corticosteroids have minimal effect on the HPA axis [16]. There are few studies and case reports suggesting that even intranasal or inhaled corticosteroids can cause HPA axis suppression. R Dixit *et al* [17] demonstrated that adrenal suppression is not uncommon with inhaled fluticasone propionate, but they used doses of >1500-2000 µg/day for 12 weeks. Arturo Loaiza-Bonilla et al reported a case of acute adrenal crisis following intranasal fluticasone propionate [18]. Deep Dutta et al reported a case of iatrogenic Cushing's syndrome following a 3-month intranasal application of steroid [19]. Femke Besemer et al identified HPA axis suppression in three of their 12 patients in the study, in which the study population was HIV infected patients using inhaled or intranasal corticosteroids. They emphasised the role of enzyme inhibitors, affecting corticosteroid metabolism, in the pathway of HPA axis suppression [20].

Even after our results of no appreciable HPA axis suppression, we would suggest that the clinical implications of adrenal suppression, particularly in the context of long-term or high-dose corticosteroid use, should not be overlooked. Subtle biochemical suppression may precede clinical adrenal insufficiency. As rare cases of adrenal crisis have been reported [18] in patients using inhaled corticosteroids, especially when combined with intranasal forms or other systemic exposures [11], one must be cautious and vigilant when using higher doses of inhaled or intranasal or both corticosteroids, especially when the person is on drugs delaying metabolism of corticosteroids. Our study results support the safety of short-term use, but clinicians should remain vigilant and may consider periodic monitoring of adrenal function in high-risk individuals or those requiring prolonged therapy.

Our study has several strengths, including its prospective design, use of both subjective and objective outcome measures, focus on real-world combined therapy and being novel in Indian settings. However, some limitations must be acknowledged. The sample size was small, having no control group and the study duration was limited to 4 weeks; thus, long-term effects on HPA axis function cannot be assessed. Being was a pilot study, it emphasises the need for further larger studies for long term assessment. Additionally, while urinary free cortisol is a reliable and simple test with medium to high sensitivity [16] and marker of basal adrenal function, dynamic testing for reserve adrenal testing, such as the ACTH stimulation test, may provide more sensitive detection of early HPA axis suppression. However, we were not able to incorporate it in our study as it was done in a resource limited setting. 24-Hour urinary free cortisol test being a non-invasive test, ease in sample collection and having medium to high sensitivity for measuring HPA axis function, was preferred over other methods such as morning serum cortisol level (low sensitivity) and ACTH stimulation (cosyntropin) test (medium sensitivity) [16]. UFC method has also been used by other researchers for measuring HPA axis suppression by fluticasone [21,22].

Conclusions

In our study, combined therapy with inhaled and intranasal fluticasone propionate administered over a four-week period resulted in significant clinical and functional improvements in patients with coexisting bronchial asthma and allergic rhinitis. Both symptom scores and spirometry parameters demonstrated meaningful gains, highlighting the efficacy of this integrated corticosteroid approach in managing unified airway disease.

Importantly, while a slight reduction in urinary free cortisol levels was observed, it was not statistically significant, and no patient developed clinically evident adrenal suppression. These findings suggest that short-term use of combined topical corticosteroids even at higher doses is not associated with significant hypothalamic-pituitary-adrenal (HPA) axis suppression in adults.

Nonetheless, clinicians should continue to monitor for potential systemic effects, particularly in patients on long-term, high-dose therapy and on drugs affecting corticosteroid metabolism. Larger, longer-duration studies including dynamic endocrine testing are warranted to further evaluate the safety profile of combined corticosteroid regimens in diverse patient populations.

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Table 1. Changes in clinical, pulmonary, and biochemical parameters from baseline to end of study.

	Baseline (mean ± SD)	End of study (mean ± SD)	p-value
TNSS	9.09±2.89	2.13±1.62	<0.05 (<0.0001)
ACT	20.48±3.07	24.09±1.12	<0.05 (<0.0001)
FVC (L) (post bronchodilator value)	3.16±0.73	3.75±0.63	<0.05 (0.0053)
FEV_1 (L) (Post bronchodilator value)	2.18±0.75	2.71±0.80	<0.05 (0.0252)
Urinary free cortisol (mcg/24 h)	31.348±9.352	28.022±9.14	0.2295

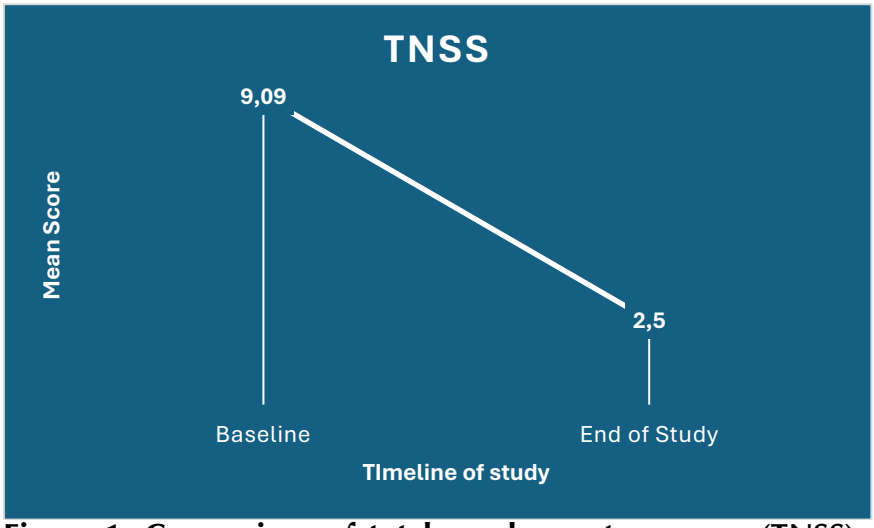

Figure 1. Comparison of total nasal symptom score (TNSS) value at the start and end of study period.

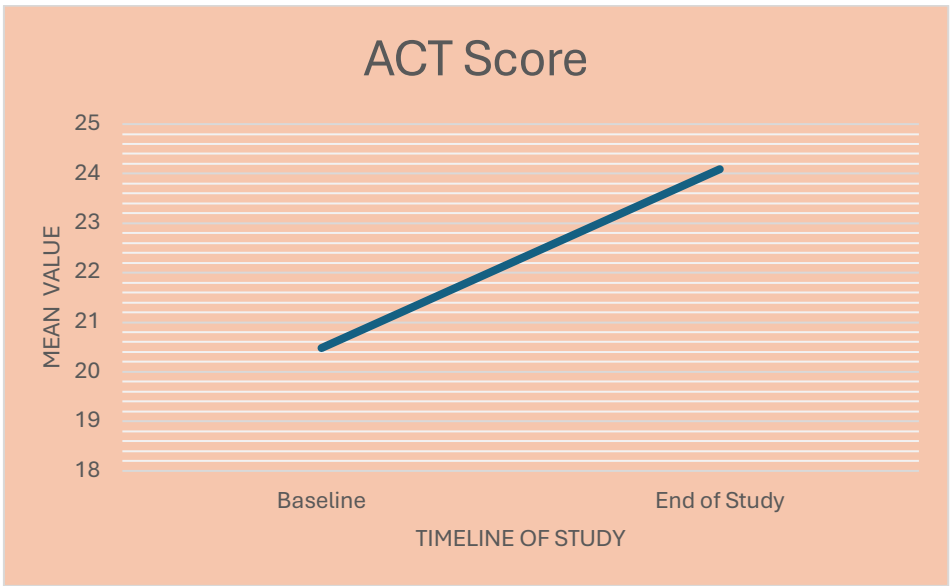

Figure 2. Comparison of Asthma Control Test (ACT) scores at the start and end of study period.

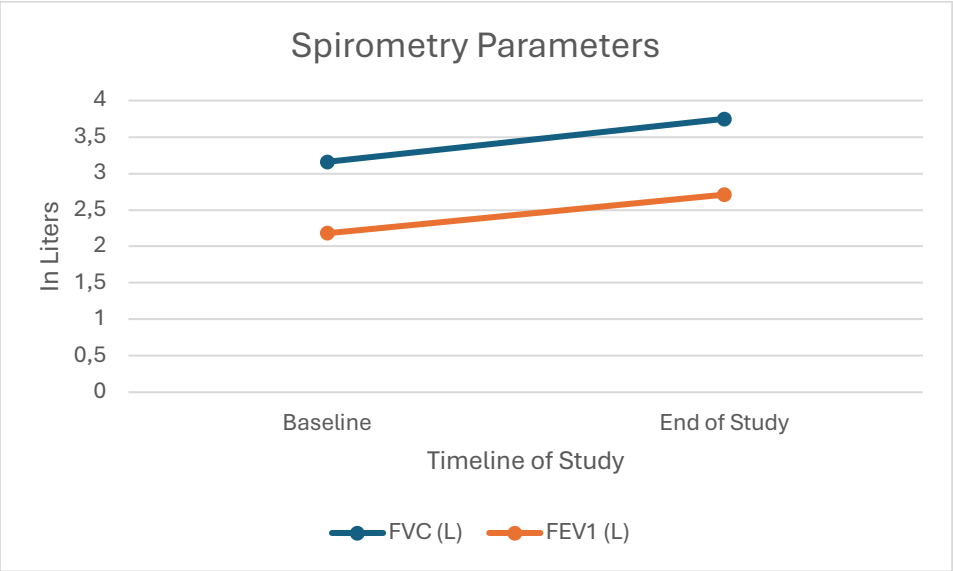

Figure 3. Comparison of spirometry parameters at the start and end of study period.