

Comparative effect of triamcinolone, nedocromil and montelukast on asthma control in children: A randomized pragmatic study

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Asthma severity can be judged by measurements of symptoms, lung function, and medication requirements. The objective was to compare the effect of a 4-wk monotherapy with low-dose triamcinolone, montelukast and nedocromil on asthma control, lung function, eosinophil blood count, and bronchial hyper-reactivity in children with mild to moderate asthma allergic to dust mite. Two hundred fifty-six children, aged 6–18 yr, with mild to moderate asthma, participated in an 8-wk study. This was a three-arm, randomized no blinding or placebo pragmatic trial comparing the effect of triamcinolone acetate (400 µg/day), inhaled nedocromil and montelukast sodium on clinical parameters of asthma [score, forced expiratory volume in 1 s (FEV₁), PC20H, and eosinophil blood count]. Two hundred forty-six children completed the study. After 4 wk of treatment with triamcinolone and montelukast, FEV₁ and PC20H significantly increased, and mean total symptoms score and mean number of eosinophil count in serum significantly decreased. Triamcinolone had a stronger effect on PC20H than montelukast. Nedocromil improved total asthma symptoms score and lung function. There was a reduction in the daytime and night-time symptom scores after treatment with all three drugs. Triamcinolone and montelukast had a stronger effect on asthma symptoms than nedocromil. There were statistically significant differences in reduction of nocturnal asthma symptoms between the triamcinolone and nedocromil groups ($p < 0.001$) and between montelukast and nedocromil ($p = 0.001$) groups, but not between the triamcinolone and montelukast groups. There was a reduction in beta-agonists use after treatment with all three drugs, with the strongest effect of triamcinolone. The study showed the strongest effect of low-dose inhaled steroids on clinical symptoms, lung function, bronchial hyper-reactivity and eosinophil blood count when compared to other asthma medications.

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Asthma is the most common chronic disease managed by pediatricians. The goals for successful management of asthma are to achieve and maintain control of symptoms, prevent asthma exacerbations, maintain pulmonary function as close to normal levels as possible, maintain normal activity levels, and prevent asthma mortality. The

management of asthma can be approached in different ways. Structured questionnaires to be filled in by the patient are used to quantify or score patients' reports of their different asthma symptoms over a period of time. Pulmonary function studies are essential for diagnosing and assessing the severity of asthma, especially in children over

5 yr, and provide an indirect assessment of airway hyper-responsiveness, which may correlate with the degree of airway inflammation (1). Eosinophil blood count has also been found to be correlated with the severity of asthma (2–4).

Although there is no cure for asthma, appropriate management leads to control of the disorder (5). Inhaled glucocorticosteroids, leukotriene modifiers, and nedocromil sodium are controller medications for the management of pediatric asthma (6).

Pragmatic trials like this seek to inform prescribers and health care planners on the most effective treatment (7).

We investigated the effect of 4-wk monotherapy with inhaled low-dose triamcinolone, montelukast and nedocromil on clinical symptoms of asthma, lung function, eosinophil blood count, bronchial hyper-reactivity, and use of beta-agonists, in children with mild to moderate asthma allergic to dust mite.

Materials and methods

Our study methods are reported in detail elsewhere (8, 9).

Patients

Two hundred fifty-six children with a typical history of asthma and sensitive to house dust

mites (*Dermatophagoides pteronyssinus* and/or *Dermatophagoides farine*) participated in an 8-wk pragmatic study. Asthma was mild to moderate, diagnosed and treated according to guidelines (6). Asthma was stable; there had been no exacerbations or need for any other treatment for 6 months, and no hospitalizations for asthma occurred within 6 months of the pre-study visit.

Male and female outpatients, aged 6–18 yr, with a clinical diagnosis of bronchial asthma with a duration of at least 6 months before the first visit were enrolled.

Study design

This was a three-arm, randomized, no blinding or placebo pragmatic trial, comparing the effect of inhaled low-dose triamcinolone acetonide (Azmacort, Aventis, Bridgewater, NJ, USA) aerosol, two puffs twice daily (400 µg/day), inhaled nedocromil (Tilade, Rhone-Poulenc), two puffs twice daily (0.002 g/puff), montelukast sodium (Singulair, MSD, Whitehouse Station, NJ, USA), 5 mg tablets in children aged 6–14 yr or 10 mg tablets in children over 14 yr of age, on clinical parameters of asthma [score, forced expiratory volume in 1 s (FEV₁), PC20H and eosinophil blood count. Figure 1 shows the flow of practices through the trial.

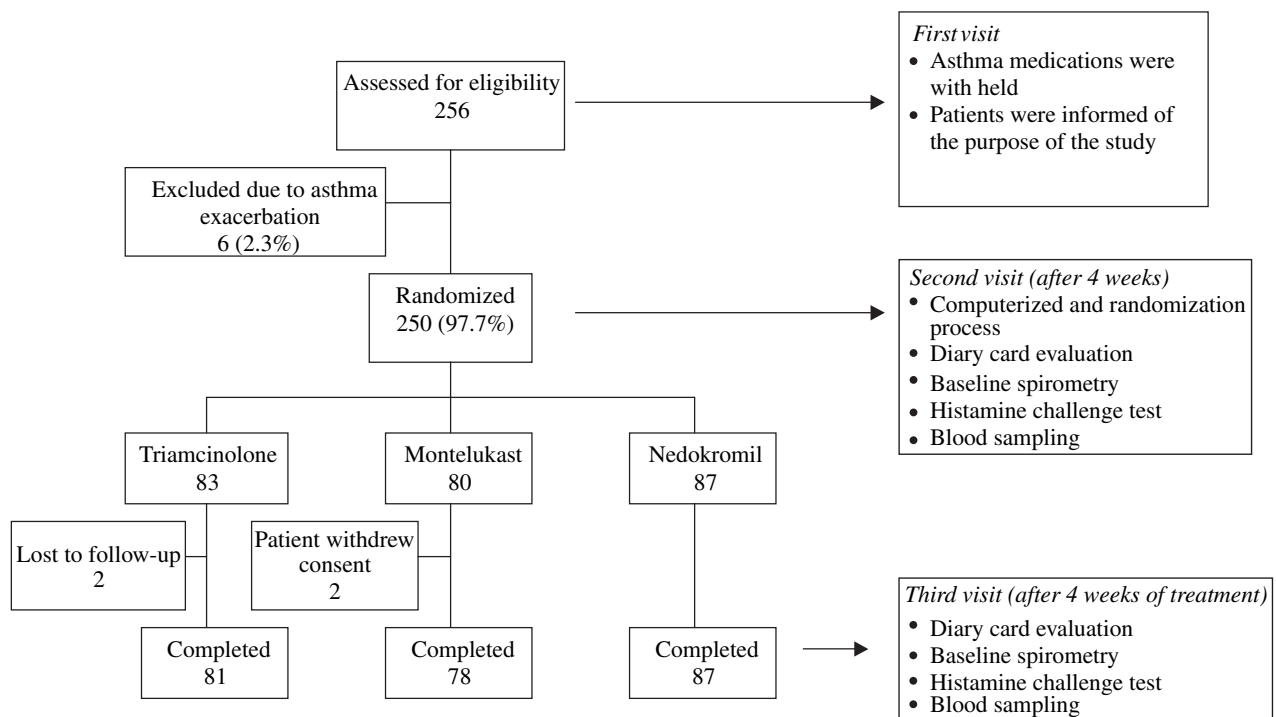


Fig. 1. Patient flow in the study.

Questionnaire

An asthma-screening questionnaire was based on the Paediatric Asthma Quality of Life Questionnaire and scales previously shown to have acceptable evaluative measurement properties (10, 11). Daytime asthma symptoms score and nocturnal awakenings were scored subjectively, each morning and evening, before and after treatment as follows: 0 for no symptoms during the day/night; 1 for symptoms, but which do not affect any activities during the day/night sleep; 2 for symptoms that affect at least one daily activity/disturb night sleep; 3 for symptoms that affect two or more daily activities/disturb sleep all night or most of the night. In addition, use of beta-agonists was scored: 0 for none, 1 for once a day, 2 for two to three times a day, 3 for more than three times a day. Total minimum score for each day was 0 (no symptoms daytime, no symptoms at night, and no need for beta-agonists) and the total maximum score was 9 (severe symptoms daytime and night and more than three uses of beta-agonists). The mean value of total score from a 1 wk period, before visit, was taken.

For example, a patient with extensive daytime symptoms had 3 points in our scale before treatment; after treatment with montelukast, improvement was moderate, up to 1 point. The total improvement in this patient, after treatment with montelukast in daytime symptoms score, was 2 points in our scale.

Lung function measurements

FEV₁ was measured by a spirometer Lungtest 1000 (MES, Krakow, Poland); the highest of three successive measurements was taken. Reference values were computed according to the recommendations of American Thoracic Society Standards of Acceptability and Reproducibility (12).

Histamine inhalation provocation tests were performed (if the pre-bronchodilator FEV₁ was 70% of predicted value) according to the method described by Cockcroft et al. (13), by using the 1-min tidal breathing method and a DeVilbiss jet nebulizer (DeVilbiss Health Care Inc., Somerset, Penn) with an output of 0.33 ml/min.

Laboratory tests

Blood samples (2 ml) were collected into serum separator tubes (S-Monovette, Sarstedt, Germany), which were allowed to stand at room temperature for 1 h, and then centrifuged at

3000 g at 4 °C for 10 min. Aliquots of serum were stored for analysis. Number of eosinophils was measured by an automated hematology analyzer K-4500 (Sysmex, Japan) and expressed as the number of cells per mm³.

Statistical methods

The results were analyzed according to well known statistical methods by using STATSOFT STATISTICA for Windows, release 6.0 (StatSoft, Inc., Tulsa, USA). All parameters were analyzed using a repeated measures analysis of variance (ANOVA). To determine differences between groups, Student's t-test, nonparametric Mann-Whitney, Wilcoxon and Fisher exact two-tailed tests were used. p-Values less than 0.05 were considered to be significant.

Ethics

The study was approved by the Medical Ethical Committee of the Medical University and all patients' parents or guardians gave their written consent for participation in this study.

Results

Two hundred forty-six children completed the study (Fig. 1). Characteristics of the patients who completed the study are given in Table 1. At the beginning of the study, symptoms score, FEV₁, PC20H, and eosinophil blood count did not significantly differ between all groups. After 4 wk of treatment with triamcinolone and montelukast, FEV₁ and PC20H significantly increased (within group) (Fig. 2), and mean total symptoms score, mean number of eosinophil count in serum significantly decreased. Nedocromil had no effect on PC20H and eosinophil count; total asthma symptoms score significantly decreased and FEV₁ significantly increased after treatment.

Triamcinolone and montelukast had a stronger effect on total asthma score than nedocromil. Only

Table 1. Patient baseline characteristics. Data are presented as mean with standard deviation (±s.d.)

	Triamcinolone	Montelukast	Nedocromil
Number of patients	81	78	87
Age (yr)	11.9 ± 1.51	12.6 ± 2.09	12.2 ± 1.70
Men gender (%)	54.32	57.69	50.57
Duration of asthma (yr)	3.7 ± 0.54	3.9 ± 0.58	3.9 ± 0.65
Asthma symptoms (score)	6.9 ± 0.99	6.6 ± 1.05	6.6 ± 1.20
FEV ₁ (% pred.)	74.3 ± 3.88	76.2 ± 5.16	75.5 ± 5.11

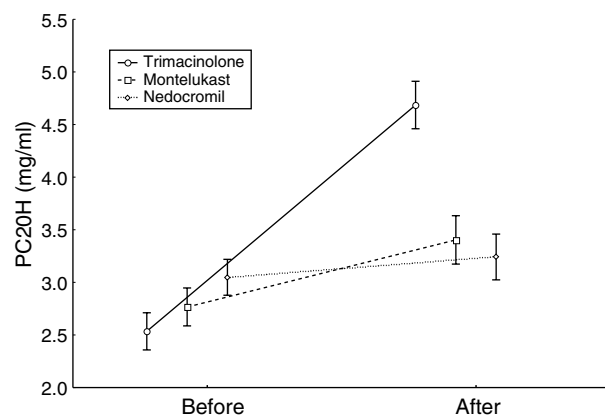


Fig. 2. Mean value and 95% confidence intervals of PC20H before (left panel) and after (right panel) treatment with triamcinolone acetoneide, montelukast sodium, and nedocromil sodium.

triamcinolone and montelukast showed the effect on eosinophil blood count. Triamcinolone had a stronger effect on PC20H than montelukast.

FEV₁ did not differ between all three groups after treatment. All data are presented in Table 2.

Daytime symptoms score

There was a significant reduction in daytime symptom score after treatment with all three drugs: triamcinolone ($p < 0.0001$), montelukast ($p = 0.002$), and nedocromil ($p = 0.009$). We did not observe statistical differences between groups in daytime asthma symptoms score reduction.

Nocturnal symptoms score

There was a significant reduction in nocturnal symptoms after treatment with all three drugs: triamcinolone ($p < 0.0001$), montelukast ($p = 0.005$), and nedocromil ($p = 0.0102$). There were statistically significant differences in nocturnal asthma symptoms between the triamcinolone and nedocromil groups ($p < 0.001$) and between montelukast and nedocromil ($p = 0.001$) groups, but not between the triamcinolone and montelukast groups.

Use of beta-agonists

There was a significant reduction in beta-agonists use after treatment with all three drugs: triamcinolone ($p = 0.002$), montelukast ($p = 0.006$), and nedocromil ($p = 0.008$). There were statistically significant differences between the triamcinolone and nedocromil groups ($p < 0.001$), between the montelukast and nedocromil groups ($p = 0.001$) and between the triamcinolone and montelukast groups ($p = 0.002$).

Discussion

Our finding that after 8 wk all three drugs, inhaled steroid in low dose, montelukast and nedocromil reduced clinical symptoms, as measured by total clinical score (daytime, nighttime symptoms and use of beta-agonist), and improved lung function, as measured by FEV₁, was unexpected. This study involved children who were left without treatment suggested by

Table 2. Effect of treatment with glucocorticoid, antileukotriene, nedocromil, placebo on total asthma symptoms score, FEV₁, PC20H and eosinophil count. Values are expressed as means with standard deviation (s.d.). Data of PC20 were assessed by geometric mean with s.d.

	Before treatment		After treatment		p-level		
	Mean	s.d.	Mean	s.d.	Within group	Versus triamcinolone	Versus montelukast
Triamcinolone							
Total asthma symptoms* (score)	6.9	0.99	3.2	1.09	<0.001	—	—
FEV ₁ (% pred.)	74.3	3.9	91.3	9.9	<0.001	—	—
PC20H (mg/ml)	2.53	0.51	4.69	1.04	<0.001	—	—
Eosinophil count (cells/μl)	347.0	116.4	233.4	94.0	<0.001	—	—
Montelukast							
Total asthma symptoms* (score)	6.6	1.05	3.6	1.34	<0.001	NS	—
FEV ₁ (% pred.)	76.2	5.2	90.5	11.8	<0.001	NS	—
PC20H (mg/ml)	2.77	0.68	3.40	1.11	<0.001	<0.001	—
Eosinophil count (cells/μl)	348.0	126.4	273.5	115.7	<0.001	NS	—
Nedocromil							
Total asthma symptoms* (score)	6.6	1.20	4.3	1.59	<0.001	0.03	0.04
FEV ₁ (% pred.)	75.5	5.1	89.6	10.0	<0.001	NS	NS
PC20H (mg/ml)	3.05	0.72	3.24	0.93	NS	<0.001	0.003
Eosinophil count (cells/μl)	345.5	107.6	301.8	105.6	NS	0.02	0.03

*Daytime, nocturnal asthma symptoms and use of β-agonists were scored as 0 (best) to 3 (worst) each.

guidelines for 8 wk and for that reason we were not able to perform this study any longer.

A study of Malmstrom revealed that beclomethasone and montelukast were identical for the first 7 wk of the trial and then begin to separate (14). Our study revealed this difference after 4 wk of monotherapy. Inhaled steroid and montelukast showed the strongest effect on reduction of nighttime symptoms. Low dose of inhaled steroid, the strongest, reduced the use of beta-agonists. There were no significant differences among the three groups in the change in FEV₁. This was not a surprise, since FEV₁, alone, especially for short periods of time, is not always a good measure of the clinical state of the patient. In CAMP study, in children with mild-to-moderate asthma, neither budesonide nor nedocromil was better than placebo in terms of lung function, but inhaled budesonide improved airway responsiveness and provided better control of asthma than placebo or nedocromil (15). It is in agreement with our findings on airway responsiveness to histamine which clearly favor inhaled triamcinolone. The use of low dose of inhaled steroid was associated with the strongest reduction in PC20H; the second strongest was montelukast. Eosinophil blood count was reduced after treatment with steroid and montelukast. The results in the nedocromil group were similar to those in the steroid and montelukast groups in clinical score and FEV₁.

In recent study by Narayanan et al., in patients given montelukast as monotherapy, asthma symptoms were well controlled at follow-up and patient satisfaction with the drug was high (16). Adelsberg et al. showed that therapy with montelukast significantly improved assessments of symptom severity as well as quality-of-life parameters for patients with seasonal allergic rhinitis (17). The leukotriene modifiers have been shown to reduce symptoms and beta-agonist use, block exercise- and cold air-induced bronchoconstriction, reduce exacerbations by 60–80% (18, 19), and nearly double symptom-free days and days without asthma (20). Additionally, some studies showed that asthmatic adolescents and children preferred treatment with tablets over the inhaled medications, resulting in better compliance (21, 22).

There are many studies exploring the clinical effects of low dose of the inhaled steroids, showing improved control of symptoms and lung function, without any long-term deterioration in the control of asthma (23–25). Kannisto et al. showed that the best combination of efficacy and safety can be achieved by using low steroid doses in school-age children with asthma. The authors

also observed unsuccessful treatment on pulmonary function and bronchodilator use in nearly 50% of the cromolyn treated children (26). In one clinical study by Konig et al., delay in starting cromolyn sodium treatment in patients treated with bronchodilators alone did result in increase of symptoms and decrease in lung function (27). Others also arrived at the same conclusion (28). However, several studies have supported the clinical efficacy of nedocromil vs. placebo in adults, as demonstrated by improvement in symptom scores, PEF, FEV₁, a reduction in rescue bronchodilator use, and inhibition of early- and late-phase pulmonary response, as well as protection against increased BHR after an allergen challenge (29–31). Edwards et al. concluded that asthma symptoms, use of bronchodilators, and lung function can be improved significantly in children recovering from an acute exacerbation of asthma or wheeze and currently receiving treatment with bronchodilators alone by the addition of inhaled nedocromil sodium (32). Our study confirmed clinical improvement after treatment with nedocromil, measured by the parameters of clinical manifestation of asthma-FEV₁ and clinical score of asthmatic well-being.

Davies et al. conducted a series of studies investigating the effects of nedocromil sodium on human bronchial epithelial cells and eosinophils *in vitro* and on eosinophils *in vivo* (33–35). Their studies confirmed that the chemotaxis and increased adhesion were blocked in the presence of nedocromil. Our results are not in accordance with those of Davies et al.; nedocromil showed no effect on eosinophil count in this population.

Conclusion

This study showed the strongest effect of low-dose inhaled steroid on clinical symptoms, lung function, bronchial hyper-reactivity, and eosinophil blood count when compared to other asthma medications. We also aver that no single conventional clinical indicator can capture important component of patient management as effectively as a validated quality-of-life questionnaire.

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