Original Article

Efficacy and Safety of Montelukast Combined with Intranasal Mometasone Furoate Versus Intranasal Mometasone Furoate Alone in Treatment of Adenoid Hypertrophy: A Randomized Controlled Trial

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ABSTRACT

Introduction: Children frequently have adenoidectomy, which has a risk of complications that include either early or late bleeding, recurrent enlargement of adenoids, and respiratory problems after surgery. Risks associated with anaesthesia are another consideration that needs to be taken into account. As a result, studies and investigations are being done into the pharmacotherapy for adenoid hypertrophy. Cysteinyl leukotriene receptor-1 modulates the inflammation process, and it has been extensively studied in the adenotonsillar tissues removed surgically from paediatric patients with obstructive sleep apnoea.

Aims/ objective: To compare the efficacy and safety of intranasal mometasone furoate alone against intranasal mometasone furoate plus montelukast combination therapy for the pharmacotherapy of adenoid hypertrophy.

Materials and Method: 50 patients were randomised in group M + M (given combination therapy of montelukast 5 mg for age ≥ 6years or 4 mg for age < 6years oral once daily + mometasone furoate 100 µg, 2 puff in each nostril) and group M (given mometasone furoate monotherapy) with 25 patients in each group. Using information from parents with special emphasis on snoring, rhinorrhoea, and mouth breathing, symptoms were scored using VAS (visual analogue scale) with scores ranging from 0 to 10. In order to conduct a clinical evaluation on each patient, radiographic testing and flexible fibro-optic endoscopic examination of the nasopharynx were also used.

Results: Patients given montelukast + mometasone furoate combination therapy for 3 months have significantly better result with respect to decrease in rhinorrhoea, mouth breathing and snoring as compared with patients given mometasone furoate monotherapy ($p<0.0001$). There was nearly 15% decline in A/N ratio in patients receiving 3 months combination therapy as compared to only 5% decrease in patients receiving monotherapy. Recurrence rate was also lower in patients receiving combination therapy.

Conclusion: Combination therapy of oral montelukast plus intranasal mometasone furoate was found to have better efficacy in patients of adenoid hypertrophy with respect to improvement in symptoms and reduction in adenoid size.

Keywords: Montelukast, Mometasone Furoate, Adenoid Hypertrophy, Leukotriene antagonist, Corticosteroid.

INTRODUCTION

Adenoid is that portion of Waldeyer's Ring that appears as a cluster of lymphoid tissue in the posterior and superior region of the nasopharynx and is crucial for the initial stages of immunity in children. It starts to expand physiologically around the ages of six to ten years, reaching its maximum size in comparison to nasopharynx volume around the age of seven, and then gradually atrophies by the age of sixteen years. [1, 2]

Among the most common pathologic diseases affecting children is adenoid hypertrophy. Based on the size of the adenoid, it results in a wide range of clinical symptoms. [3] Persistent or recurring infections are among the most typical signs of pathologic and physiological adenoid alterations. 4 When a child's nasal airway is blocked by adenoid hypertrophy, it can result in serious symptoms and side effects like enuresis, delay in physical and cognitive development, and cardio-respiratory abnormalities. [5]

The adenoid is regarded as a component of the mucosa-associated lymphoid tissue, and being subjected to several antigens through the nasal and oral cavities causes early childhood development of naturally acquired immunity, which leads to the generation of B-cells that lead to the formation of IgG, IgM, and IgA plasma cells. [1, 6] Because of its gateway location in the upper respiratory system, the adenoid acts as a storehouse for bacteria and viruses that cause repeated infections and result in lymphoid hyperplasia. Adenoid hypertrophy can also result from allergic inflammation, in which many mast cells that are IgE-positive accumulate in adenoid tissue. [1, 6, 7]

Adenoidectomy is among the most frequent surgical treatment performed on children because persistent blocked nasal passages brought on by an enlarged adenoid is among the most prevalent paediatric problems that might be linked to chronic sinusitis and recurrent otitis media. [8] The adenoid tissue's high concentration of glucocorticoid receptor-α and cysteinyl leukotriene receptor-1 facilitated non-operative therapy using nasal steroid sprays and montelukast. [1, 9]

The most popular techniques for diagnosing adenoid enlargement are nasal endoscopy and lateral radiography. [10] Children frequently have adenoidectomy, which has a risk of complications that include either early or late bleeding (4%–5%), recurrent enlargement of adenoids (10%–20%), and respiratory problems after surgery (27%).[11] Risks associated with anaesthesia are another consideration that needs to be taken into account.[12] As a result, studies and investigations are being done into the pharmacotherapy for adenoid hypertrophy.[13]

Along with reducing oedema and vascular permeability, intranasal steroids have a considerable local impact on the generation and/or activation of a number of pro-inflammatory agents in the nasal mucosa. The stimulation of the immune system seen in enlarged adenoid tissue may be lessened by this potent anti-inflammatory action. [14] Intranasal administrations of mometasone, a strong 17-heterocyclic corticosteroid, results in increased binding to corticosteroid receptors, poor systematic concentration (0.1%), and significant first pass metabolism. The hypothalamo-pituitary axis is not suppressed when normal intranasal doses are being used. [15]

The primary mediators of inflammation in the respiratory system are leukotrienes. Such mediators frequently play a role in the development of paediatric illnesses like bronchial asthma Additionally, they play a systemic and local role in the inflammatory process that results from adenoid hypertrophy.[11] Cysteinyl leukotriene receptor-1 modulates the inflammation process, and it has been extensively studied in the adenotonsillar tissues removed surgically from paediatric patients with obstructive sleep apnoea.[16] An oral cysteinyl leukotriene receptor antagonist called montelukast is utilised for the prevention of bronchial asthma and allergic rhinitis. On the basis of the recent finding of enhanced expression of cysteinyl leukotriene receptors in adenotonsillar tissues of children with sleep apnoea, it has also been investigated for the pharmacotherapy of adenoid hypertrophy in several clinical studies. [17]

The purpose of this study was to compare the efficacy and safety of intranasal mometasone furoate alone against intranasal mometasone furoate plus montelukast combination therapy for the pharmacotherapy of adenoid hypertrophy.

MATERIALS AND METHODS

This was an open label randomised controlled trial with parallel 1:1 allocation conducted in department of ENT of tertiary care hospital of eastern India from March 2022 to February 2023 after getting approval from Institutional Ethics Committee. The study was conducted under the guidelines of good clinical practice and declaration of Helsinki after providing and explaining participant information sheet and taking written informed consent from the patients or their parent/guardians.

Inclusion Criteria: Patients of age-group of 3 to 12 years; patient having sign and symptoms of adenoid hypertrophy such as mouth breathing, habit of snoring, chronic rhinorrhoea; patients with diagnosis of adenoid hypertrophy confirmed by radiography and adenoid/nasopharynx ratio (A/N) greater than 50%; patients with grade 3 or 4 adenoid hypertrophy on endoscopic examination.

Exclusion Criteria: Patients having any systemic disease or otitis media or acute upper respiratory tract infection; patients with craniofacial anomalies; patients who have undergone adenoidectomy or adenotonsillectomy previously; patients allergic to Mometasone or Montelukast; patients with history of use of any corticosteroids or leukotriene antagonists within 1 month of enrolment.

With anticipated 10% decrease in A/N ratio in patients receiving combination therapy and 7% decrease in patients receiving mometasone furoate monotherapy, minimum sample size required with 90% power and 0.05 alpha value was found to be 42 with 21 patients in each group. To compensate for expected attrition, we planned to recruit 50 patients.

50 patients were randomised in group M + M (given combination therapy of montelukast 5 mg for age ≥ 6years or 4 mg for age < 6years oral once daily + mometasone furoate 100 µg, 2 puff in each nostril) and group M (given mometasone furoate monotherapy) with 25 patients in each group. Randomisation was done using web generated random numbers.

Each participant in the current research got a thorough clinical evaluation, which included a full clinical and otorhinolaryngological examination as well as a detailed history taking. Using information from parents with special emphasis on snoring, rhinorrhoea, and mouth breathing, symptoms were scored using VAS (visual analogue scale) with scores ranging from 0 to 10. The nasal passages and nasopharynx were examined using a flexible fibro-optic endoscope, and the degree of adenoid hypertrophy was assessed using Cassano et al.'s categorization. [18] They classified choanal blockage into four grades:

Grade I: 0%–25% obstruction

Grade II: 25%–50%

Grade III: 50%–75%

Grade IV: 0%–100%

To evaluate the patency of the airways, lateral neck radiographs were taken with the neck extended and the mouth open. According to Fujioka et al.'s approach, the adenoidal/nasopharyngeal ratio (A/N ratio) was determined. [19] According to this method, (A) denotes the distance between the spot of greatest convexity of the adenoid shadow and a line that runs along the anterior border of the basiocciput. (N) is the measurement of the separation that exists between the anteroinferior margin

of the sphenobasioccipital synchondrosis and the posterior margin of the hard palate.

To determine the efficacy, all patients had undergone examinations and evaluations after 3 months of therapy and to determine the recurrence, all patients again undergone examination after treatment discontinuation for a further three months. The examination included a symptom evaluation using the same 0–10 scale that was first employed. In order to conduct a clinical evaluation on each patient, radiographic testing and flexible fibro-optic endoscopic examination of the nasopharynx were also used. Any adverse event that appeared to be causally related to mometasone or montelukast were also noted.

Statistical Analysis: Data collected from patients were compiled in a tabular form using Microsoft Excel 2019. Scores of patients' symptoms, and A/N ratio were expressed as mean and standard deviation (SD) and unpaired t-test was used to test statistical significance of difference between group M and group M + M. Sex, age group, adverse events and adenoid grade were expressed as frequency and percentage and Fisher's exact test or Chi-square test was used to evaluate statistical significance of difference between group M and group M + M. A p-value of less than 0.05 was taken as the measure of statistical significance.

RESULTS

25 patients were enrolled in each group. 1 patient in group M + M and 2 patients in group M were lost to follow up in first month of study. So, assessment was done on 24 patients of group M + M and 23 patients of group M.

Table 1: Comparison of baseline demographic and clinical characteristics between group M and group M + M

Variables	Group M + M (n = 24)	Group M (n = 23)	P-Value
Age Group, n (%)			
3-5 Years	6 (25.00)	5 (21.74)	0.91*
6-9 Years	11 (45.83)	10 (43.48)	
10-12 Years	7 (29.17)	8 (34.78)	
Sex, n (%)			
Male	19 (79.17)	18 (78.26)	>0.99**
Female	5 (20.83)	5 (21.74)	
Mean symptom score (out of 10) in mean ± SD			
Rhinorrhoea	8.57±0.81	8.59±0.90	0.94***
Mouth Breathing	7.51±0.69	7.58±0.83	0.75***
Snoring	7.45±0.67	7.56±0.78	0.61***
Adenoid/Nasopharynx Ratio in mean ± SD	66.57 ± 5.95	68.45 ± 8.02	0.36***
Adenoid Grade, n (%)			
Grade 3	17 (70.83)	15 (65.22)	0.76 (Fisher's Exact Test)
Grade 4	7 (29.17)	8 (34.78)	

*(Chi-Square Test) **(Fisher's Exact Test) ***(Fisher's Exact Test)

There was no statistically significant difference between two groups with respect to age, sex, mean symptom score with respect to rhinorrhoea, mouth breathing or snoring, A/N ration, and adenoid grade (p>0.05).

Table 2: Comparison of mean symptom score and adenoid/nasopharynx ratio between group M and group M + M after 3 months of treatment

Variables	Group M + M (n = 24)	Group M (n = 23)	P-Value
Mean symptom score (out of 10) in mean ± SD			
Rhinorrhoea	5.55±0.62	7.01 ± 0.81	<0.0001
Mouth Breathing	4.91±0.58	5.96 ± 072	<0.0001
Snoring	4.39±0.53	5.73 ± 0.69	<0.0001
Adenoid/Nasopharynx Ratio in mean ± SD	51.14±4.76	62.27±7.48	<0.0001

Patients given montelukast + mometasone furoate combination therapy for 3 months have significantly better result with respect to decrease in rhinorrhoea, mouth breathing and snoring as compared with patients given mometasone furoate monotherapy (p<0.0001). There was nearly 15% decline in A/N ratio in patients receiving 3 months combination therapy as compared to only 5% decrease in patients receiving monotherapy.

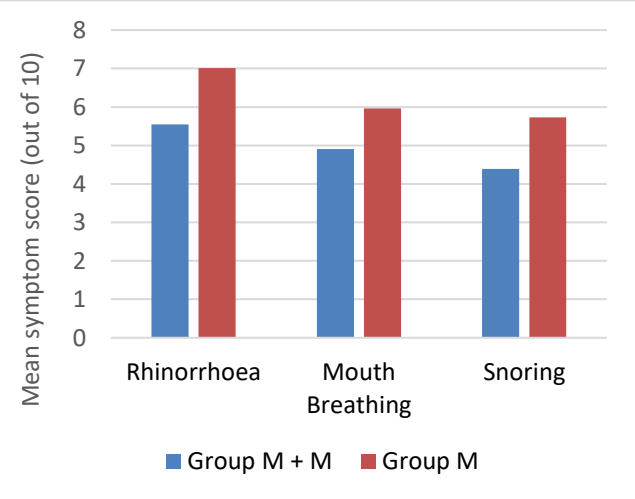

Figure 1: Comparison of Mean Symptom Score Between Two Groups

Table 3: Comparison of mean symptom score and adenoid/nasopharynx ratio between group M and group M + M after 6 months (3 months of stoppage of drugs)

Variables	Group M + M (n = 24)	Group M (n = 23)	P- Value
Mean symptom score (out of 10) in mean ± SD			
Rhinorrhoea	6.17±0.65	7.73±0.89	<0.0001
Mouth Breathing	5.29±0.61	6.87±0.83	<0.0001
Snoring	5.08±0.58	6.65±0.78	<0.0001
Adenoid/Nasopharynx Ratio in mean ± SD	57.35 ± 5.12	65.25 ± 7.77	0.0002

After 3 months of stoppage of drugs, patients who were given combination therapy reported less recurrence with respect to symptoms of rhinorrhoea, mouth breathing and snoring as compared to patients given monotherapy.

Table 4: Comparison of adenoid grade by endoscopic examination between group M and group M + M

Variables	Group M + M (n = 24)	Group M (n = 23)	P- Value
After 3 months of treatment			
Grade 2	16 (66.67)	12 (52.17)	0.44 (Chi-Square Test)
Grade 3	7 (29.17)	8 (34.78)	
Grade 4	1 (4.17)	3 (13.04)	
After 6 months (3 months of stoppage of drugs)			
Grade 2	13 (54.17)	9 (39.13)	0.18 (Chi-Square Test)
Grade 3	10 (41.67)	9 (39.13)	
Grade 4	1 (4.17)	5 (21.73)	

66.67% of patients in group receiving combination therapy moved to adenoid grade 2 as compared to only 52.17% in group receiving monotherapy after 3 months of pharmacotherapy. Only 1 patient was in grade 4 in group receiving combination therapy after 3 months of stoppage of drugs as compared to 5 patients in monotherapy group.

Table 5: Comparison of adverse events causally related to Montelukast or Mometasone

Variables	Montelukast	Mometasone	P-Value
Headache	4	6	0.61
Cough	2	5	
Nausea/Vomiting	0	3	
Conjunctivitis	0	1	
Pharyngitis	0	1	

Headache was more frequent adverse event causally related to both mometasone furoate and montelukast. Montelukast was found to have better safety profile as compared to mometasone.

DISCUSSION

Adenoid tissue can expand as a result of infections or persistent irritation. In addition to the hazards associated with general anaesthesia, adenoidectomy surgery carries some additional risks, including bleeding, infections, and palate disorders. [20] The likelihood of these side effects and the prevalence of adenoid hypertrophy recurrence prompted the demand for conservative medical management involving anti-inflammatory and anti-allergic drugs.

In comparison to other steroids used intranasally, mometasone furoate nasal spray has a diminished bioavailability, high first pass metabolism, and a somewhat greater affinity for binding to the receptor for glucocorticoid. [21] Numerous studies on the effects of nasal steroids, notably nasal mometasone furoate for the pharmacotherapy of adenoid enlargement, have been published in the literature. Intranasal mometasone furoate appears to have some positive effects on some outcomes of nasal blockage brought on by adenoidal hypertrophy, according to several investigators. [22-24]

In their systematic review and meta-analysis, Chohan et al. found that intranasal mometasone improved quality of life and improvement for all nasal symptoms. [25] They also suggested conducting additional randomised controlled studies to examine the safety and effectiveness of mometasone in children with adenoid enlargement. Unlike intranasal mometasone, the administration of oral montelukast in the treatment of adenoid hypertrophy has received relatively little research. In their study of the impact of oral montelukast on the size and signs and symptoms of adenoid enlargement, Shokouhi et al. came to the conclusion that montelukast, an anti-inflammatory drug, showed significant efficacy in reducing adenoid volume and relieving the associated clinical signs and symptoms.[11]

In order to assess the impact of oral montelukast, intranasal mometasone furoate, and combination therapy on adenoid size, Tuhanolu et al. conducted a randomised prospective clinical study. However, they did not evaluate the rate of recurrence after stoppage of pharmacotherapy and instead suggested studies with larger sample size for different doses and duration of therapy.[20]

In the present research, we have done comparative assessment between intranasal mometasone furoate monotherapy and combination therapy of intranasal mometasone furoate and oral montelukast for the pharmacotherapy of adenoid enlargement, evaluating the effectiveness and rate of recurrence after stopping the drug therapy. The groups being researched were similar in their ages and genders. In this research, we evaluated the patients using both subjective and objective metrics. At the time of the initial assessment, there were no significant differences between the two groups of participants in terms of the primary symptom scores, the adenoid/nasopharynx ratio, or grade of adenoid enlargement.

In this research, we have done comparative assessment of the scores of the primary symptoms of rhinorrhoea, breathing through the mouth, and snoring between the two groups three months after the start of pharmacotherapy according to the subjective evaluation. Patients getting the oral montelukast plus intranasal mometasone combination therapy had statistically significant improvements in scores.

In accordance with the objective evaluation, we have done comparative evaluation with respect to the endoscopic adenoid hypertrophy grading and the alteration in adenoid/nasopharynx ratio. By doing comparative

evaluation of the endoscopic grade of hypertrophy of the adenoid after three months of therapy, this research found that 66.67% of patients getting combination therapy advanced to adenoid grade 2, compared to only 52.17% of patients receiving monotherapy. After 3 months of drug discontinuation, only 1 patient in the combination therapy group was in grade 4, compared to 5 patients in the monotherapy group.

In this research, we evaluated how the A/N ratio changed in each group throughout the course of the study. According to our findings, patients who received montelukast + mometasone combination therapy improved more quickly in terms of the A/N ratio, with a statistically significant difference (P<0.001).

In Bhargava and Chakravarti's study, the baseline mean adenoid size was reduced after 6 months of therapy with intranasal mometasone monotherapy. The authors allocated 30 patients to the study who had been diagnosed with otitis media with effusion and adenoid enlargement. [24]

Subjectively, we evaluated the main symptom scores after another three months after stopping medications, and we found that patients receiving montelukast plus mometasone combination therapy had higher scores with statistically significant differences. Objectively, participants getting montelukast + mometasone combination therapy had statistically better outcomes with respect to adenoid/nasopharynx ratio after the same follow-up time after stopping medication. (P < 0.001). We found that most of the patients didn't show significant enlargement of adenoid size.

Our study had certain limitations such as limited number of patients, exclusion of patients with upper respiratory tract infection and otitis media and craniofacial anomalies. Drug interactions with other concomitant medications was also no taken into account.

CONCLUSION

According to findings of this study, combination therapy of oral montelukast plus intranasal mometasone furoate was found to have better efficacy in patients of adenoid hypertrophy with respect to improvement in symptoms and reduction in adenoid size. In comparison to monotherapy with intranasal mometasone furoate, combination therapy after adding montelukast led to superior subjective and objective improvements after three months of pharmacotherapy and reduced recurrence following cessation of drug therapy for another 3 months. To ascertain the fate of the adenoid following medical therapy, additional researches with an extended follow-up time are necessary.

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