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Do leukotriene inhibitors/modifiers reduce symptoms associated with Nasal Polyps?

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ABSTRACT

Objective: The objective of this systematic review is to determine how well leukotriene inhibitors/modifiers reduce symptoms associated with nasal polyps.

Study Design: The studies included in this review are three randomized controlled trials.

Data Source: The three RCTs in this review were obtained by performing a PubMed search using the keywords “nasal polyp”, “leukotriene”, and “Montelukast”. All articles were published in English and in peer-reviewed journals.

Outcomes Measured: The three studies determine whether there was significant improvement of symptoms in patients with nasal polyps who were treated adjunctively with leukotriene inhibitors/modifiers. The symptoms were measured before and after the treatments using three different symptom score guidelines.

Results: Patients who were diagnosed with chronic rhinosinusitis with nasal polyposis who were given Montelukast (leukotriene inhibitor) as adjunctive therapy demonstrated statistically significant reduction in symptoms, $p<0.05$. In all three studies, Wu et al[10], Yelverton et al[11], Suri et al[12] the symptom scores decreased significantly in comparison to patients who received no Montelukast adjunctive therapy.

Conclusions: Based on the systematic review of the three randomized controlled trials, one can decisively say that leukotriene inhibitors/modifiers (Montelukast) can reduce the symptoms associated with the presence of nasal polyps. All three studies verified statistically significant reduction in symptoms compared to the control groups.

Key Words: Leukotriene, Nasal Polyps, Montelukast

INTRODUCTION

Nasal polyps are noncancerous growths inside the nose or sinuses which can cause or exacerbate a variety of symptoms.[1] Their development can be linked to chronic inflammation, autonomic nervous system dysfunction, and genetic predisposition.[1] However, a definitive pathogenesis of these polyps has yet to be discovered.[1] Theories state that nasal polyps arise from conditions leading to chronic inflammation of the nasal mucosa such as allergic states or recurrent infection.[1] The nasal polyps most commonly discussed are benign semitransparent lesions which arise from the mucosa of the nasal cavity or from the paranasal sinuses.[1] They are usually found at the outflow tract of the sinuses and can result in symptoms such as rhinorrhea, congestion, postnasal drip, anosmia, facial pain or headache, or snoring.[1] Children with chronic sinusitis, cystic fibrosis, allergic rhinitis, and allergic fungal sinusitis are more likely to have multiple nasal polyps. [1]

Nasal polyps are relevant to the physician assistant practice because they affect 1-4% of adults and 0.1% of children in the United States.[1] Patients affected with the symptoms of nasal polyps will first present to a primary care practice, a field containing a large portion of all physician assistants.[1] They have increased occurrence in men and usually manifest after 20 years of age, if they are benign.[1] The incidence of cystic fibrosis patients with nasal polyps ranges between 6-48%.[1] The polyps obstruct the outflow tract of the sinuses leading to recurrent sinus infections or allergic rhinitis.[1] Nasal polyps are relevant to patients because those affected will have multiple doctor appointments and days of work/school missed a year.[1]

Nasal polyps themselves do not require treatment.[2] The infections which result because of their obstruction is what costs the most.[2] It is estimated that sinusitis costs the U.S. $6 billion

every year to treat.[2] Therefore if 1-4% of the population has nasal polyps, recurrent sinusitis treatment could cost over $240 million a year.[2] Patients with nasal polyps will have recurrent sinusitis which ends up costing them even more.[2] Recurrent outpatient visits lead to accumulation of various medications and antibiotics which, without health insurance, can become costly.[1] Once the decision is made to remove the nasal polyps through endoscopic nasal surgery, it can cost the patient thousands depending where the patient receives surgery.[2]

Chronic sinusitis is responsible for 16 million outpatient visits a year.[3] Therefore, it can be estimated that patients with symptomatic nasal polyps lead to 160,000-640,000 outpatient visits a year.[3] This results in countless hours lost and work days missed.[3] The diagnosis of nasal polyps is not always easy especially if they cannot be visualized on physical exam.[3] Due to this, patients come back for more outpatient visits for recurrent symptoms.[3] If a patient decides to undergo endoscopic sinus surgery to remove the nasal polyps, they could end up missing up to a week of work.[3]

The exact cause or pathogenesis behind nasal polyps is unknown.[4] However, most theories reveal they are caused by a reaction to allergies, inflammation, and rarely, cystic fibrosis.[4] Nasal polyp formation usually takes place in the middle meatus.[4] The meatus becomes edematous due to fluid collection which leads to a polypoidal change.[4] This change develops the new sessile polyps.[4] They become pedunculated and obstructive after excessive sneezing, rhinorrhea, and time, due to gravity.[4] Nasal polyps present most commonly in patients with chronic rhinosinusitis but are also associated with other diseases such as asthma, aspirin-exacerbated respiratory disease, cystic fibrosis, allergic fungal sinusitis, Kartagener's syndrome, Young's syndrome, eosinophilic granulomatosis with polyangiitis, and nasal mastocytosis.[5]

The methods used to treat nasal polyps are aimed at reducing the symptoms that they exacerbate or the underlying inflammation.[6,7] For example, one of the most commonly used medications for treating the intranasal inflammation are topical nasal steroid sprays with triamcinolone, budesonide, or fluticasone.[6,7] If the exacerbation is severe, oral corticosteroids may also be given such as oral prednisolone, methylprednisolone, or dexamethasone.[6,7] To relieve any itching or rhinorrhea a medical provider could prescribe any antihistamine such as diphenhydramine, cetirizine, loratadine, or fexofenadine.[6,7] To relieve symptoms such as sinus congestion, decongestants such as phenylephrine or pseudoephedrine can be prescribed.[6,7] Some medical providers will prescribe cromolyn sodium for a patient with excessive inflammation for which intranasal steroid treatment failed or is contraindicated.[6,7] Leukotriene inhibitors/modifiers such as Zafirlukast, Montelukast, or zileuton have recently become an adjuvant medication for nasal polyp associated symptoms, and are the medical therapy in question in this review.[8] Finally, if the symptoms are persistent and cannot be controlled, patients have an option to undergo endoscopic sinus surgery or polypectomy.[8]

Patients with nasal polyp obstruction have difficulty finding the right medications to continually treat their chronic symptoms. [9] Leukotriene inhibitors or modifiers are an adjunct medication option for patients with chronic sinusitis with nasal polyposis. [9] Leukotrienes act to sustain inflammatory reactions in the body such as asthma and allergies. [9] Leukotriene receptor antagonists such as Zafirlukast or Montelukast can bind to the receptors to block the inflammatory response leukotrienes perpetuate. [9] The blocked inflammatory response will reduce the symptoms identified as being problematic with nasal polyps.[9]

OBJECTIVE

The objective of this systematic review is to determine whether leukotriene inhibitors/modifiers reduce symptoms associated with nasal polyps.

METHODS

The three studies included in this review are all randomized control trials. [10-12] The studies were included because all patients were 18 years old or older, had been diagnosed with chronic rhinosinusitis with nasal polyposis, and were willing to participate in any imaging studies. [10-12] The studies were also included because they compared leukotriene inhibitors as adjunctive medical therapy versus a steroid based medical regimen that excluded leukotriene inhibitors.[10-12] Patients excluded from these studies were ones who used oral/nasal steroid or immune-modulators in the past 4 weeks prior to the study. [10-12] Patients were also excluded if they had a history of acute infection, antrochoanal polyps, cystic fibrosis, fungal sinusitis, or gastroesophageal reflux disease. [10-12] Patients who had only unilateral polyps or history of sensitivity to protocol drug regimen were also excluded.[10-12] Suri et al also excluded those with recent nasal surgery.[12]

All three studies included symptom score reports proving significance to the patient population. [10-12] The articles were published in English, in peer-reviewed journals, and were investigated for inclusion in this review, by the author. Keywords for the PubMed and EBSCOhost search were “leukotriene”, “nasal polyp”, and “Montelukast”. [10-12] From that selection, the three articles included were chosen based on relevance to topic and outcomes which mattered to patients. [10-12] The three articles included were all published after 2014 and excluded patients under18 years old, patients with a contraindication to steroid intake, or patients with a sensitivity reaction to any of the medication regimen. [10-12] All statistics reported for the articles used p-value. [10-12] The demographic and characteristics are included below. [10-12]

Table of demographics and characteristics of included studies (Table 1)

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Wu, (2016) [10]	RCT	31	25-62	Patients ≥18 years old with the diagnosis of chronic sinusitis with NPs based on history, nasal endoscopy, and CT scan	Patients who used oral/nasal steroid or immune-modulators in the past 4 weeks prior to endoscopic surgery, had a history of acute infection, antrochoanal polyps, cystic fibrosis, fungal sinusitis, or gastroesophageal reflux disease	0	Combined budesonide spray (Rhinocort Aqua) plus LTRA Montelukast (Singulair) 10 mg once daily
Yelverton, (2016)[11]	RCT	27	18-76	Patients >17 with chronic sinusitis with NPs who had no Montelukast therapy for at least 1 month.	Patients with cystic fibrosis, a fungal ball, or on a tapered prednisone regimen	0	Post endoscopic sinus surgery regimen with added on Montelukast 10mg
Suri, (2015)[12]	RCT	40	24-58	Patients who agreed to undergo an ENT examination and CT scan of paranasal sinuses, and nasal endoscopy	Patients who had only unilateral polyps, current steroid intake, nasal surgery, or history of sensitivity to protocol drug regimen	0	Oral steroid prednisolone 35mg with nasal steroid budesonide (2 metered doses) with orally administered Montelukast 10mg

OUTCOMES MEASURED

The outcomes measured in these three studies were the improvement of symptoms post medication regimen. [10-12] Patients were asked to score their symptoms before and after the regimen.[10-12] Each study used a different symptom score report. [10-12] These symptom score reports are Total Nasal Symptom Score (TNSS), Sino-Nasal Outcome Test (SNOT-20), and International Classification of Sinus Disease (ICSD). [10-12] Before the patients began treatment, intervention investigators also used the Lund-Kennedy Score System to determine polyp size, the Lund-Mackay to determine the polyp location, or endoscopy to determine the level of obstruction caused by the nasal polyps.[10-12]

Wu et al used the Lund-Kennedy scoring system prior to treatment to determine polyp size before medical intervention. [10] Participants scored their current symptoms using the TNSS. [10] This study then compared two groups, the control group, which received combined budesonide spray (hinocort aqua) alone and the experimental group which received combined budesonide spray (rhinocort aqua) plus Montelukast (singulair) 10 mg once daily. [10] After this intervention, the patients scored their symptoms using the TNSS. [10] The TNSS rates nasal congestion, runny nose, nasal itching, sneezing, or difficulty sleeping on a scale of none, mild, moderate, and severe. [10] The TNSS also rates the symptoms presence within 12 hours and within 2 weeks.[10]

Yelverton et al used the Lund-Kennedy and Lund-Mackay scoring systems to determine the size and location of the nasal polyps. [11] Before beginning the medical regimen, the patients scored their symptoms using SNOT-20. [11] The control group received a routine post endoscopic sinus surgery steroid based regimen while the experimental group used the same regimen with 10mg on Montelukast as adjunct therapy. [11] They used the SNOT-20 patient symptom scoring system again to compare their course of intervention. [11] The SNOT-20 ranks sneezing, urge to

blow nose, runny nose, cough, post-nasal discharge, thick nasal discharge, ear fullness, dizziness, ear pain, facial pain/pressure, difficulty sleeping, fatigue, mood changes, and disruptions with work on a scale from very mild, mild, moderate, severe, to worst.[11]

Suri et all used endoscopy to determine the size and placement of the nasal polyps.[12] They gave the control group oral steroid prednisolone 35mg with nasal steroid budesonide (2 metered doses).[12] The experimental group was given the same regimen with additional orally administered Montelukast 10mg.[12] They used ICSD before and after the intervention. [12] ICSD evaluates and rates patient's symptoms of facial pain and pressure, headache, nasal blockage, congestion, nasal discharge, anosmia, and discomfort on a 0-10 scale, 10 being the worst.[12]

RESULTS

In the study conducted by Wu et al, the TNSS symptom score total was used to determine the reduction of symptoms in the experimental group compared to the control group.[10] The reduction was determined to be statistically significant.[10] Before beginning their specific treatment regimens, the mean symptom score for the control group was 6.65 and the mean TNSS score the experimental group was 6.24.[10] The mean change from baseline is greater for the experimental group treatment than for the control group (Table 2).[10] This indicates the experimental group had overall less symptoms or a greater reduction in overall symptoms than the control group had after the medical intervention.[10] The p-value result was determined to be statistically significant at $p<0.01$.[10] The results from this randomized controlled trial are listed below in Table 2.[10]

Table 2: Mean Change from Baseline, Wu et al[10]

	TNSS Score Before Treatment	TNSS Score After Treatment	Mean Change from Baseline

Control Group	6.65*	5.8*	-0.85
Experimental Group	6.24*	3.0*	-3.24

*$p<0.01$

In the study conducted by Yelverton et al, the SNOT-20 symptom score method showed the difference in results between the control group and the experimental group to be statistically significant.[11] The participants were separated into groups after having completed the original questionnaire before the medical intervention.[11] After the treatment regimen, the symptom score results for the experimental group were over four times better than the score for the control group (Table 3).[11] The p-value was determined to be statically significant at <0.001 and the confidence interval as determined to be at 95%.[11] The results are listed below in Table 3.[11]

Table 3: Mean change from baseline, Yelverton et al[11]

	SNOT-20 Score Before Treatment	SNOT-20 Score After Treatment	Mean Change from Baseline
Control Group	29.53*	25.61*	-3.92
Experimental Group	29.53*	13.25*	-16.28

*$p<0.001$

In the study conducted by Suri et al, the ICSD symptom score total was used to determine the reduction of symptoms in the experimental group compared to the control group as statistically significant.[12] The groups were separated and asked to complete the questionnaire before and after the medical intervention.[12] The questionnaire was filled out at 8 weeks and then again at 12 weeks.[12] After 12 weeks, the total mean change from baseline was greater for the experimental group than for the control group.[12] The p value for the 8 weeks mean change from baseline was 0.0006 and for 12 weeks it was 0.0034.[12] The results are listed below in Table 4.[12]

Table 4: Mean Change in Baseline, Suri et al[12]

	ICSD Score Before Treatment	ICSD Score After Treatment-Week 8	ICSD Score After Treatment-Week12	Total Mean Change from Baseline
Control Group	7.5*	5.2*	5.8*	-1.7
Experimental Group	7.9*	4.1*	4.8*	-3.1

*$p<0.05$

DISCUSSION

The three randomized controlled trials discussed in this review suggest that leukotriene inhibitors/modifiers are effective adjunctive therapy for the management of symptoms associated with nasal polyps.[10-12] All three of these studies demonstrated statically significant reductions in their outcomes measured along with a statistical significance threshold set at $p<0.05$.[10-12]

The randomized controlled trial by Suri et al recorded the symptom scores at 8 weeks and then again at 12 weeks.[12] At 12 weeks the symptom score worsened overall but the score for the leukotriene inhibitor as adjunctive therapy remained lower than the score without the leukotriene inhibitor.[12] This means that although the symptoms reappeared some on week 12, the addition of the leukotriene inhibitor, Montelukast, was still the more effective treatment.[12]

It is also important to note that some of the participants in the study by Yelverton et al had endoscopic sinus surgery before participating in the randomized controlled trial.[11] However, the patients were still considered patients in the category of chronic rhinosinusitis with nasal polyposis since they had received this diagnosis prior.[11] The basis for using patients who had received endoscopic polyp removal surgery was that patients who experience nasal polyposis are at risk for having recurrent symptoms after their surgery.[11] These patients are also at risk for having the polyps grow back because they have predisposition to them on a on a cellular level.[11]

The studies all showed statistically significant reduction of symptoms using leukotriene inhibitor/modifiers.[10-12] However, there is some question as to whether additional therapy influences compliance. [10-12] The leukotriene inhibitor was an additional medication to the steroid therapy, so the experimental groups received twice as many medications as the control groups.[10-12] In these studies, although, compliance was not listed as an issue.[10-12]

The Wu et al and Suri et al included baseline location and size measurements but none followed up with the polyps after treatment. [10,11] In future studies, it would be beneficial to redo these measurements after the interventional treatment. This would have been valuable to this review as well, because the reduction in size of the polyps could have led to the decreased symptoms.

These studies included very minimal reported data. All three RCTs used mean change from baseline and p values to determine the significance of Montelukast on the associated symptoms of nasal polyposis. [10-12] There should have been more information reported such as the decreased size of nasal polyps for example. The studies could have benefitted from reporting more information/ data results to make their claim that symptoms had been reduced greater in the experimental groups. The patient reporting was excellent regarding determining significant outcomes for patients. [10-12] However, more data to prove changes in the nasal mucosa or other ways to represent quality of life should have been used to verify the data provided by patient symptom scores. Lack of back up results makes the overall outcome of the review a weaker conclusion.

CONCLUSION

Leukotriene inhibitors/modifiers decrease the symptoms associated with nasal polyps. They are almost always given as an adjunctive medication instead of monotherapy. The steroid therapy which leukotriene inhibitors/modifiers are added to is effective at treating the symptoms alone. [10-12] However, symptoms decreased even more so with the addition of a leukotriene inhibitor/modifier. [10-12] Patients with nasal polyps will benefit from the addition of leukotriene inhibitors/modifiers to their medical regimen. [10-12] In the future, any trials planning to determine the effectiveness of medications on patients with nasal polyps could benefit from focusing solely on the reduction of size of the polyps. The reduction of polyp size would reduce obstruction and should theoretically reduce symptoms. There are still many discoveries to be made about the development of nasal polyps as well as the most effective away to handle the symptoms that they cause.

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