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Efficacy of Verapamil in Chronic Rhinosinusitis with Nasal Polyposis: A Double-Blind and Placebo-Controlled Randomized Clinical Trial

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Abstract

Background: P-glycoprotein 1 (permeability glycoprotein, abbreviated as P-gp or Pgp also known as Multi Drug Resistance protein 1 (MDR1) or ATP-Binding Cassette sub-family B member 1 (ABCB1) or Cluster of Differentiation 243 (CD243) is a new non-invasive diagnostic biomarker for therapeutic purposes in determining chronic rhinosinusitis endo types. Inhibition of this membrane transporter by verapamil has been recently used as a therapeutic target.

Methods: We enrolled 36 patients between 18 to 55 years old with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) in a double-blind, placebo-controlled, randomized clinical trial. Patients in both group received similar treatment with intranasal mometasone and irrigation. In addition, the intervention group received 80 mg verapamil tablets three times daily for three months and the control group received placebo. Primary and secondary outcome measures such as Sino-Nasal Outcome Test (SNOT-22) and Lund-Mackay Score (LMS) assessed at the onset and the end of the intervention. The differences of quantitative variables between groups were evaluated by independent samples t-test and Mann-Whitney test. Paired-samples T test was performed to test the difference between two measurement times in each group. Chi-square and Fisher's exact test were used for qualitative variables. Analysis of Covariance (ANCOVA) was performed to evaluate the differences between the intervention and control groups before and after the intervention.

Results: The mean of $SNOT_{22}$ after intervention ($SNOT_2$: N Second measurement of $SNOT_{22}$) for intervention group was 29.88 ± 18.80 and for control group was 52.27 ± 19.10 and the mean of LMS after intervention (LMS 2: Second measurement of LMS) for intervention group was 16.11 ± 6.99 and for control group was 16.77 ± 5.69. ANCOVA showed a significant change for $SNOT_{22}$ between two groups (P=0.001), and β= -20.580 given the placebo group as the reference category, so the mean values of $SNOT_{22}$ significantly decreased in intervention group compared to placebo group but no significant change occurred in LMS between two groups (P=0.784).

Conclusion: In this study, we determined that p-gp inhibitors such as verapamil improve subjective symptoms like $SNOT_{22}$ score, but we did not achieve any significant impact on objective measures.

Keywords: Chronic Rhinosinusitis (CRS); Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP); Verapamil; Lund-Mackay Score (LMS); Sino-Nasal Outcome Test ($SNOT_{22}$); Endotype; Permeability-glycoprotein (p-gp)

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Introduction

Chronic Rhinosinusitis (CRS) is a common disease with constellations of symptoms and significant effect on quality of life of the patients. It is one of the most common causes of prescription of antibiotics in the community. Direct costs are the expenses related to multiple visits, prolonged and repeated need to use various antibiotics and different diagnostic strategies. Indirect costs include lost work performance, absenteeism, reduced productivity and poor quality of services resulting from overtime fatigue. Despite the high prevalence of this disease, its pathogenesis is still

unknown [1,2].

CRS is divided into two main clinical phenotypes based on the presence or absence of nasal polyps. CRS with Nasal Polyposis (CRSwNP) is one of the most challenging diseases to treat because of chronic inflammation with lifelong need to medical and repeated surgical treatment. Endotyping of CRS aims to optimize and individualize the treatment in order to avoid under- and over-treatment, and to avoid the necessity of repeated surgery, multiple courses of oral glucocorticoids and also reduce the financial implications of CRS for the society. Patient selection based on inflammatory endotypes, which are often defined by the presence or absence of one or more biomarkers, offers a more accurate definition than the phenotype alone. Also, endotyping can be classified into three inflammatory endotypes (type 1, 2, or 3) based on a unique signature profile composed of specific immune cells, inflammatory mediators and physiologic functions, including type 1 based on IFN-γ, IL-12 expression, the association of Th1 cytokine pattern, the contribution of NK cells and CD8 T-cells and its role in intracellular immunity against viruses, type 2 based on IL-4, 5, 13 expressions, the association of Th2 cytokine pattern, the contribution of eosinophil, mast cell, basophil and its role in host immunity against parasites and allergic diseases and type 3 is based on IL-22, IL-17 expression, the association of Th17 cytokine pattern, the contribution of neutrophil and its role in immunity against bacteria and extracellular fungi [3-6]. CRSwNP is commonly associated with type 2 inflammation. The use of inflammatory endotypes are limited to guide the selective treatment in CRS because there is no precise and standard definition for each endotype, the prediction of clinical signs and symptoms based on inflammatory endotypes is not yet clear, and the level of inflammatory mediators varies not only from person to person but also from different anatomical sites [3]. Other biomarkers in CRS include clinical phenotype, age, and comorbid asthma. The type of symptoms and their severity vary in different patients, so it can be used to predict therapeutic responses and as a non-invasive method to determine inflammatory endotypes for treatment selection. A recent study evaluating phenotypes and endotypes in CRS patients showed a significant association between specific clinical manifestations and specific inflammatory profiles. For example, lack of smell and purulent nasal discharge is associated with type 2 and 3 inflammations. Thus, the clinical phenotype may replace the prediction of inflammatory endotypes. Age as a factor in different studies found that older patients with CRS were more likely to have a neutrophilic response than younger patients. So drugs that may target type 2 inflammation are potentially less effective in older people. As another biomarker, comorbid asthma is associated with type 2 inflammatory endotype and more severe sinonasal disease in CRSwNP. 48% of CRSwNP patients have comorbid asthma. The use of clinical phenotypes is limited to guide the selective treatment in CRS because there are no clinical signs or symptoms for endotype 1 and 3; also, symptoms are subjective, change over time, and it is not known whether inflammatory endotypes change or remain constant concomitant with clinical signs and symptoms changes [3,7]. The third approach to guide in CRS management is clinical biomarkers. There are no known clinical biomarkers of type 2 inflammation in CRSwNP or types 1 and 3 in CRSsNP or CRSwNP, but eosinophils and IgE have been studied as potential biomarkers of type 2 inflammation in CRSwNP as a predicting factor for disease severity and therapeutic responses. Limitation of clinical biomarkers in CRS management include that peripheral blood eosinophil counts and IgE levels are less subjective than clinical symptoms, and there is no specific cut off point in the distinction between groups of responder and non-responder [3,7-9].

Glucocorticoids are widely used in CRS, and not intended as therapeutic targets because the exact mechanism of steroid immunosuppression in CRS is still unknown. On the other hand, prolonged use of oral corticosteroids accompanies unacceptable side effects. Therefore, the lack of immunological evidence associated with potential morbidity in steroid usage and the limitations of inflammatory endotypes, clinical phenotypes, and traditional clinical biomarkers have led to further research on new pathophysiological mechanisms for alternative therapies with high efficacy less side effects. This strategy requires finding a new diagnostic non-invasive biomarker for therapeutic purposes that can be used alone or in combination with other traditional biomarkers in determining endotype, accurate diagnosis, ideal treatment [3,7,10,11].

Permeability-glycoprotein (p-gp) is one of these biomarkers, which is a potential factor in the pathogenesis of CRSwNP. In recent years, many studies have been performed on this membrane transporter protein. In the field of sinonasal diseases, it has been used as a biomarker, and the inhibition of this pump has been used as a therapeutic target. Over the past decades, adjuvant chemotherapy research has led to identifying several generations of p-gp inhibitors. Verapamil is one of the first known p-gp inhibitors [7,12,13]. Macrolides and triazoles are other drugs that can inhibit p-gp [14,15]. Verapamil is a calcium channel blocker that binds to the L-Type (cav1) voltage-dependent calcium channel, blocking calcium release into host cells and increasing the relaxation of heart cells and smooth muscle cells. It is commonly used to treat hypertension, angina, and cardiac arrhythmias [13]. Because verapamil is safely used to treat cluster headaches (dose of verapamil in cluster headache = 240 mg to 320 mg per day) in healthy people, it may be a reasonable candidate for clinical trials for chronic rhinosinusitis. Based on the safe dose of 240 mg per day, which is the minimum allowable dose in healthy people, it seems to be free of side effects [16].

Materials and Methods

This double-blind, placebo-controlled, randomized clinical trial study was performed at department of allergy and clinical immunology, Hazrat-e-Rasool Hospital, Iran University of medical sciences. This study included 36 patients between 18 to 55 years old with moderate to severe (baseline SNOT-22 Score ≥ 20) CRSwNP based on EPOS consensus criteria [17]. The sample size was calculated according to the study of Bleier et al. in 2017 [18].

Exclusion criteria were the presence of comorbidities like gastrointestinal hypomotility, liver failure, kidney disease, muscular dystrophy, pregnant or nursing females, heart failure, hypertrophic cardiomyopathy, atrial and ventricular arrhythmia, HR<60 or SBP<110 or DBP<70, and patients taking the following medications; Beta-blockers, Cimetidine, Clarithromycin, Erythromycin, Cyclosporin, Digoxin, Disopyramide, Diuretics, Flecainide, HIV Protease Inhibitors (Indinavir, Nelfinavir, Ritonavir), Quinidine, Lithium, Pioglitazone, Rifampin and systemic corticosteroids usage from a month ago.

Patients in both equal randomly intervention and control groups (n=18) received similar treatment with intranasal mometasone (FDA approved Intranasal corticosteroid) and nasal irrigation. In addition, the intervention and control groups received 80 mg oral verapamil tablets three times daily and placebo, for 12 weeks, respectively. The randomization was based on ZIP code and random allocation

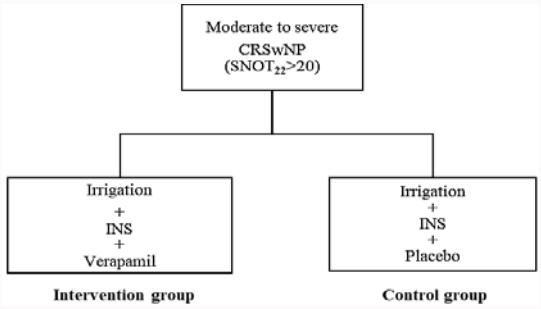

Figure 1: Flowchart of trial.

software. The minimum dose of verapamil was given to patients based on the safety dose used for individuals with cluster headaches, defined as 80 mg oral verapamil tablets three times daily. Placebo had the same characteristic as oral verapamil tablets (size, color, and taste). Drug and Placebo were produced in AlborzDaroo pharmaceutical company in Iran. At the beginning of the study, all patients were assessed by taking a history, physical examination. Evaluation for age, sex, Body Mass Index (BMI), history of previous sinus surgeries (0, 1, and more than 1), concomitant asthma, hypersensitivity to NSAIDs (Non-steroid Anti Inflammatory Drugs), smoking, total serum IgE, blood and nasal secretions eosinophilia, and olfactory dysfunction was done. The primary outcome measure was the $SNOT_{22}$-questionnaire that is validated in Farsi [19]. The secondary outcome measure was objective sinonasal symptoms on Lund- McKey Score (LMS). The $SNOT_{22}$-questionnaire completion and perform coronal sinonasal CT scans were done at the onset and end of the intervention to determine primary and secondary outcome measures, which higher scores show a worse outcome. Two unrelated specialists also performed LMS interpretation. Figure 1 shows the flowchart of the trial.

Statistical Analysis

The results were expressed as mean and Standard Deviation (mean ± SD) for normal distributed quantitative variables and median (Interquartile range), frequency (percentages) for qualitative variables. The normality of quantitative variables was tested with Shapiro-Wilk test. The mean differences between groups were evaluated by independent samples T-test and U Mann-Whitney. Chi-square and Fisher's exact tests were performed for qualitative variables. Paired-samples T Test was performed to test the difference between two measurement times in each group. ANCOVA was used to estimate the treatment effect in this randomized clinical trial study with a pre- and a post-treatment measures. A p-value of less than 0.05 was considered significant. The data were analyzed using SPSS 21.

Results

The intervention group consisted of 9 males and nine females with a mean age of 40.11 ± 6.30 years (range: 29 to 51 years); the control group consisted of 12 males and six females with a mean age of 37.72 ± 7.29 years (range: 22 to 49 years). During the 90 days, no patient from the intervention and control group discontinued the study, and no drug reaction or complication was observed among patients. Baseline clinical characteristics of the two groups were shown in Table 1. This shows that there is no statistically significant difference between the two groups before the intervention, so both groups were homogeneous. The mean of $SNOT_{22}$ before intervention ($SNOT_1$) for intervention group was 53.44 ± 14.61 and for control group was 57.11 ± 15.45 which there was no significant difference between two groups (p=0.470). The mean of LMS before intervention (LMS1) for intervention group was 15.50 ± 5.32 and for control group was 16.61 ± 4.96 which there was no significant difference between two groups (p=0.522).

The mean of SNOT1 in the intervention group with 53.44 ± 14.61 and the mean of $SNOT_2$ ($SNOT_{22}$ after intervention) in this group was 29.88 ± 18.80 which showed a significance difference between two times in this group (P<0.001). The mean of LMS1 in the intervention group was 15.50 ± 5.32 and the mean of LMS2 (LMS after intervention) in this group was 16.11 ± 6.99 with p=0.463. For control group the values of $SNOT_{22}$ before and after placebo were 57.11 ± 15.45 and 52.72 ± 19.10 respectively (P=0.071) and the values of LMS before and after placebo were 16.61 ± 4.96 and 16.77 ± 5.69 respectively (P=0.886). After performing analysis of covariance for the two variables $SNOT_{22}$ and LMS, there was a significant change for $SNOT_{22}$ between two groups (P=0.001), and β= -20.580 given the placebo group as the reference category, so the mean of $SNOT_{22}$ after intervention had been significantly decreased in intervention group. But there was no significant change in LMS after intervention between two groups (P=0.784) (Table 2 and Figure 2).

Discussion

In this study, we aimed to evaluate verapamil's efficacy as a p-gp inhibitor in CRSwNP patients using primary outcome measures such as $SNOT_{22}$ score and secondary outcome measures such as LMS. Patients in the intervention group but not in the control group had a significant statistical change from baseline in the $SNOT_{22}$ score at 12 weeks, indicating the efficacy of verapamil on subjective symptoms as the primary outcome measure in CRSwNP disease. Patients in the intervention or control group did not show a statistically significant change from baseline in LMS at 12 weeks, indicating that verapamil did not improve objective signs such as LMS as a secondary outcome measure. The effect of the drug on the $SNOT_{22}$ score was significant between two groups of intervention and control. There was no significant effect of the drug on LMS between them. In another study in Massachusetts that examined the effect of oral verapamil in 18 patients with CRSwNP over eight weeks, both subjective and objective measurements [$SNOT_{22}$ score and LMS but not Lund-Kennedy endoscopic Score (LKS)] showed significant differences between the verapamil and placebo groups. However, in our study, the subjective measurement improved in the opposite of the objective one, i.e., LMS [18].

P-gp in sinonasal epithelium as a membrane transporter and efflux pump, it regulates cell membrane permeability to drugs, toxins, metabolites, and cytokines, prevents the accumulation of intracellular metabolites and xenobiotics [20]; as an immunomodulator modulates the immune responses by regulating the secretion of cytokines and chemokines, which are essential in both T-cell activation and dendritic cell migration. P-gp overexpression in CRSwNP affects local cytokine environments by releasing cytokines through the potential non-classical mechanism in the sinonasal epithelium and independently regulates Th2-induced inflammation and eosinophilic recruitment. The hypothesis for the efficacy of verapamil in CRSwNP, which is used as a calcium-blocker in heart diseases, include a P-gp inhibitor modulates the induced Th2-related cytokines [21-26]. In one study, this drug was able to block the secretion of IL-5 and IL-6, and it was concluded that verapamil reduces the secretion of Th2-related cytokines in sinus polyps [27]. It is also used as an immunomodulator in inhibiting Th2-dependent inflammation in asthma [28]. Also, p-gp

Table 1: Comparison of risk factors between intervention and control groups in patients with CRSwNP before the intervention.

Groups/Variables	Intervention (n=18)	Control (n=18)	p-value
Sex (Male/Female)	9/9 (50%/50%)	12/6 (66.7%/33.3%)	0.31
Age (years)	40.11 ± 6.30	37.72 ± 7.29	0.301
BMI (kg/m^2) Median(IQR)	25.65 (5.25)	37.50 (8.00)	0.788
Blood eosinophilia (cell/mm^3)	503.11 ± 338.90	635.44 ± 373.71	0.274
SNOT1(SNOT$_{22}$ pre-intervention)	53.44 ± 14.61	57.11 ± 15.45	0.47
LMS1(LMS pre-intervention)	15.50 ± 5.32	16.61 ± 4.96	0.522
Nasal smear for eosinophil (cell/HPF) Median(IQR)	35 (75)	40 (72.50)	0.412
Total serum IgE (ku/l)Median(IQR)	96.00 (307.25)	123 (248.50)	0.729
Sinus surgery (number) 0	3 (16.7%)	8 (44.4%)	0.173
1	8 (44.4%)	5 (27.8%)	
>1	7 (38.9%)	5 (27.8%)	
Concomitant asthma	12 (66.7%)	14 (77.8%)	0.457
Concomitant NSAIDs hypersensitivity	10 (55.5%)	7 (38.9%)	0.317
Severe olfactory disorder or lack of smell	15 (83.3%)	15 (83.3%)	0.999
No olfactory or mild olfactory dysfunction	3 (16.7%)	3 (16.7%)	
Smoking	2 (11.1%)	1 (5.5%)	0.999

Table 2: Clinical and imaging data in intervention and control groups of patients with CRSwNP before and after the intervention.

Group/Variables		Intervention (n=18)	Control (n=18)	*P-value (ANCOVA Results)
SNOT$_{22}$ score	Before	53.44 ± 14.61	57.11 ± 15.45	0.001
	After	29.88 ± 18.80	52.72 ± 19.10	
P-value		<0.001	0.071	
LMS	Before	15.50 ± 5.32	16.61 ± 4.96	0.784
	After	16.11 ± 6.99	16.77 ± 5.69	
P-value		0.463	0.886	

*P-value Between Groups
Data are shown with Mean ± SD

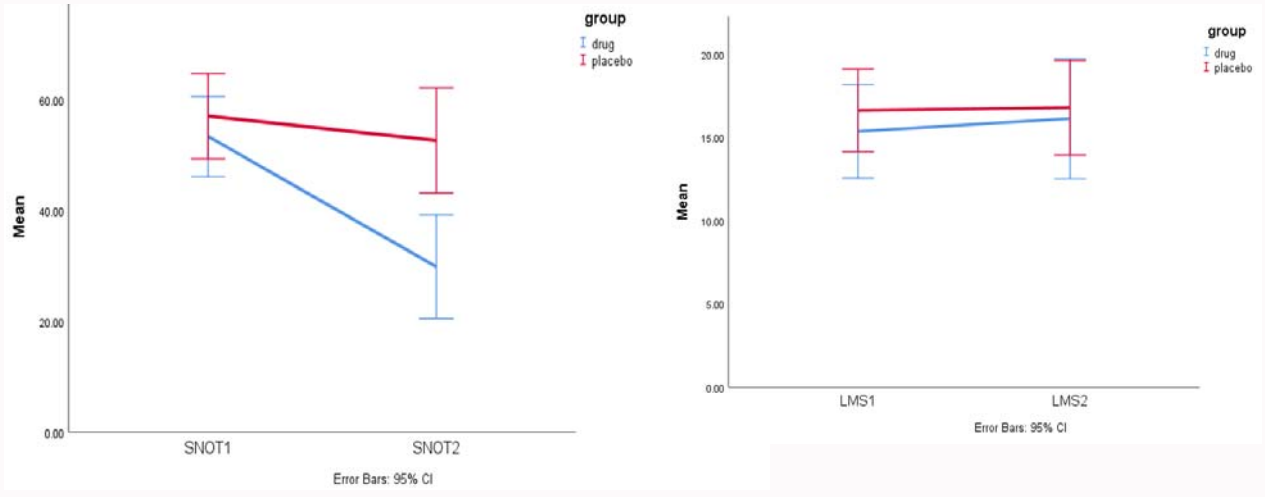

Figure 2: Primary and secondary outcome measures for all patients (intervention and control groups) with CRSwNP. SNOT$_1$: Pre-treatment SNOT$_{22}$, SNOT$_2$: Post-treatment SNOT$_{22}$, LMS$_1$: Pre-treatment LMS, LMS$_2$: Post-treatment LMS.

can regulate the intracellular storage of drugs such as corticosteroids in mucosal epithelial cells. It has been hypothesized that overexpression of p-gp in CRSwNP causes resistance to corticosteroids due to their limited intracellular retention. Verapamil, as a p-gp inhibitor, causes corticosteroid to remain longer within epithelial cells of the polyp. As a result, clinical responses to corticosteroids will be affected by concomitant use of verapamil, synergizing verapamil, and glucocorticoid effects [29-34], as we used Intranasal Corticosteroid (INS) with verapamil in our trial and found the synergism effect of verapamil on INS in improving subjective symptoms. Therefore, the effect of p-gp inhibitors such as verapamil may indicate a novel and safe target therapy in CRS patients, especially CRSwNP who have

eosinophilic inflammation, Th2 skewed, and p-gp overexpression. They may have the same efficacy of corticosteroids or biologic agents at safe doses used in healthy people [3,5,7,10]. In our study, no side effects were observed with this dose of verapamil during the trial. It can also be an economically viable drug compared to biologics in CRS patients. Also, the reason for the not improvement in LMS measurement, despite a significant improvement in subjective measurements, maybe due to the short period between pre-and post-treatment paranasal sinus CT scan, given that structural changes due to mucosal damage or possibly fibrosis requires a long time, which requires further research in this area.

Various studies have shown that known markers of clinical severity predict p-gp expression in CRS. As mentioned earlier, due to the limitations of inflammatory endotypes, clinical phenotypes, and clinical biomarkers in CRS management, sometimes a combination of several biomarkers is necessary to determine inflammatory endotypes and plan for the ideal treatment strategy [3]. For example, a blood eosinophil count or tissue eosinophilia can identify most CRSwNP patients in a clinical setting, along with a clinical history of asthma, allergy, and/or AERD (Aspirin Exacerbated Respiratory Disease) [35]. Therefore, we are looking to combine traditional, new, and comorbid biomarkers to identify type 2 inflammatory endotype in sinonasal polyps [3,5,6,8]. If we overview our trial factors, including blood or tissue eosinophilia, total serum IgE, comorbid asthma, AERD, olfactory disorder, and total serum IgE, we find that these biomarkers are more in favor of type 2 inflammation. As a result, we are considering the significant relationship between these biomarkers and verapamil treatment response, indicating confirmation of type 2 inflammatory and p-gp overexpression.

Conclusion

Chronic rhinosinusitis with nasal polyps is a heterogeneous disease with unknown pathogenesis and many therapeutic challenges; therefore, it imposes direct and indirect costs on the patients, requires further research to identify and use alternative therapies with better clinical impact and fewer side effects. It requires sufficient information about the pathophysiology of the disease and the mechanism of action of these factors. The investigation of novel pathophysiologic mechanisms paves the way for finding non-invasive diagnostic biomarkers and therapeutic targets for them. Patient selection based on the inflammatory endotype, optimize and individualize the treatment in order to avoid under- and over-treatment, and to avoid the necessity of repeated surgery and multiple courses of oral glucocorticoids, reduce the financial implications of CRSwNP for the society.

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