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Original Article

The association of serum immunoglobulin E levels on outcomes of maximal medical therapy among patients of chronic rhinosinusitis

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Abstract:

Background: Chronic rhinosinusitis (CRS) is one of the highest prevalent diseases affecting a large population with significant impact on quality of life (QoL) and health care burden. It is almost universally accepted that before surgical therapy is considered, maximal medical therapy (MMT) should be used. Serum immunoglobulin E (IgE) level is a valuable diagnostic parameter in the severity of CRS patients. If relationship between outcomes of medical therapy with different levels of pretreatment Ig E levels can be established, then it may be use as a predictive factor to prioritize between medical treatment or surgery among CRS patients.

Objectives: This study aims to see whether the pretreatment serum immunoglobulin E (IgE) levels of patients with Chronic rhinosinusitis (CRS) have any association on the outcomes of maximal medical therapy (MMT).

Methods: This quasi-experimental study was conducted in the Department of Otolaryngology-Head & Neck Surgery, BSMMU, Dhaka from March 2017 to July 2019. Seventy cases of CRS were assigned into three groups based on pretreatment IgE level: normal (≤ 25 IU/ml), moderately raised (>25 to ≤ 149 IU/ml), and high (>150 IU/ml). Outcomes were measured by evaluation of changes in Pre- and Post-MMT-Rhinosinusitis Disability Index (RSDI) and Lund-Mackay (LM) staging of HRCT- PNS.

Results: The pre-treatment and post-treatment mean of RSDI and LM scoring indicated a significant difference between normal and moderately raised groups. But High IgE showed no significant statistical differences between pretreatment and post treatment mean RSDI and LM scoring.

Conclusion: Patients of chronic rhinosinusitis with normal and moderately raised pretreatment serum IgE levels were significantly responded to maximal medical therapy. Whereas patients with high level of IgE had poor improvement with maximal medical therapy.

Keywords: Chronic Rhinosinusitis, IgE, Lund-Mackay scoring, RSDI, QoL.

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Introduction:

Rhinosinusitis is defined as an inflammation of the nose and the paranasal sinuses, characterized by two or more symptoms, like nasal blockage, congestion, nasal discharge, with or without facial pain/pressure, with or without reduction or loss of smell and either endoscopic signs of nasal polyps, and/or mucopurulent discharge primarily from middle meatus and/or oedema or mucosal obstruction primarily in middle meatus and/or CT changes (mucosal changes within the ostiomeatal complex and/or sinuses). Chronic rhinosinusitis (CRS) is

defined as a presence of two or more of the above symptoms for 12 or more weeks¹

The etiology is complex and multifactorial, comprising infection, host systemic disorders, anatomic variations, and other causes in which atopy is included²⁻³. Several studies show that, it is characterized by local eosinophilic inflammation with high production of immunoglobulin E (IgE), as well as interleukin-5 (IL-5) and interleukin-21 (IL-21) and eosinophilic cationic protein. Specially presence of IgE in tissue and serum are marked in CRS which does not increase in relation to seasonal allergen exposure in patient with CRS¹⁻⁶. IgE determination is valuable in the diagnostic assessment of patients with established or suspected allergic diseases⁷. Correlation between total IgE levels and the thickness of sinus mucosa on computed tomography (CT) imaging in CRS patient has also been described⁸. A widely accepted Radiological staging system of rhinosinusitis also established, known as Lund-Mackay (LM) scoring⁹. It is generally accepted that the treatment of CRS should begin with medical therapy and that surgical procedure should be undertaken only after failure of medical therapy. "Maximal medical therapy" (MMT) generally centers on oral

antibiotics as the mainstay of treatment, also includes oral steroids, topical nasal steroids, nasal saline irrigation, and other treatments¹⁰⁻¹² and it aims to reduce mucosal inflammation and swelling, control infection, and restore aeration of the nasal and sinus mucosa and improve quality of life and prevent disease progression or recurrence¹³⁻¹⁴. Various researchers of different countries suggested an association of the levels of IgE before or after MMT. Lemos-Rodriguez et al. 2017 reported IgE levels seem to have a significant association with the quality of life (QoL) or outcomes of MMT in the patients with CRS¹⁵. However, the presence of nasal allergies regardless of IgE levels frequently recommend for surgery after MMT. In the patients with higher-IgE levels (≥ 150 IU/ml), MMT seemed to fail at high rates with or without the presence of polyps or allergic disease and frequently indicated for surgical intervention.

Symptoms of CRS are associated with the significant debilitating physical

symptoms and disruption of quality of life (QoL). Correct utilization of the prescribed medication may not be a major issue in short-term treatment but represents a key factor for obtaining control by MMT beyond several weeks. Adherence, prejudices about treatment, fear of adverse events and economic reasons are considered key factors in determining whether a patient would take the prescribed medication. The aim of this study is to evaluate whether serum immunoglobulin E (IgE) level have association with the response to maximal medical therapy in patient of chronic rhinosinusitis or not. So, prediction of outcome of medical therapy can be done accordingly to reduce dependency on medical therapy, thus reducing the side effects of drugs and cost burden for medicine and reducing undue delay for surgical intervention. As far as literature reviews are concerned, no such study has been conducted

in Bangladesh. So, this study might be helpful in making rational decisions in clinical practices and form a background for further study and using serum IgE as a marker for disease severity and hence to determine the possible need for surgery

Methods:

This quasi-experimental study was carried out in the department of Otolaryngology-Head & Neck Surgery at BSMMU, from March 2017 to July 2019 after the approval of the institutional review board (IRB) of BSMMU. Patients with subjective evidence with symptoms (EP3OS criteria) and objective evidence of CRS on either nasal endoscopy or radiographic imaging were selected purposively. Inclusion criteria were diagnosed case of CRS based on either symptoms or nasal endoscopy or radiographic imaging, age >18 to <60 years and patients who gave consent willingly for the study. Patients with history of taking oral steroids or antibiotics in the previous 2 months, history of allergic fungal sinusitis, systemic vasculitis, primary ciliary dyskinesia, granulomatous disease, history of cocaine abuse, or cancer, and patients who was pregnant or breast-feeding and Comorbidities like DM, CKD, CLD, immune compromised patients were excluded. After taking informed written consent, detail history taking, and physical examination of each patient were performed. A semi-structured case record form was used as a questionnaire (instrument) to interview and to collect data. Serum IgE titers were done in every patient and they were assigned to three different groups based on the pretreatment levels of serum IgE. Group I: patients with levels of IgE of ≤ 25 IU/ml were assigned to the normal-IgE group, group II: IgE levels of >25 to ≤ 149 IU/ml were assigned to the moderately raised IgE group, and group III: ≤ 150 IU/ml were assigned to the high-IgE group. HRCT of paranasal sinus with bone

window without contrast imaging done in every patient. To assess QoL in the three groups, we used the Rhinosinusitis Disability Index (RSDI) at their initial visit and after completion of treatment. Higher scores on the RSDI represented greater disease severity. Then MMT were set as 4 weeks of antibiotic, topical steroid spray, short term systemic steroid, nasal decongestant, and antihistamine therapy. The patients were prescribed oral Cefuroxime axetil 500 mg taken twice a day for 4 weeks, oral steroid (prednisolone), beginning with 1mg/kg daily dose initially and tapered gradually for 4 weeks were given. All the patients were received isotonic saline solution nasal rinses and topical nasal steroid sprays for twice daily and non-sedative antihistamine throughout the intervention period. Patient compliance was evaluated by mid-treatment visit and an exit survey at their follow-up post-MMT visit to verify whether they fully completed the treatment. After completion of treatment HRCT of PNS was done again to compare with pretreatment scan. For objective radiologic assessment, we used the LM (Lund-Mackay) grading system to evaluate all sinuses CT's obtained at pre- and post MMT visits. The mean change in LM and RSDI scores were calculated by subtracting the post-MMT scores from the pre-MMT scores. Paired Student's t-tests were used to compare LM and RSDI score differences in the two groups; $p < 0.05$ at 95% CI were considered as the level of significant.

Results:

Among 70 patients, 12 (17.14%) were 18-25 years of age, 34 (48.57%) were 26-35 years, 16 (22.86%) were 36-45 years and 8 (11.43%) were 46-60 years old. Age range was 18 and 50 years. Forty (57.14%) subjects were male and 30 (42.86%) were female. Among them 22 (31.43%) cases were from rural area, 33 (47.14%) were from urban area and 15 (21.43%) from slum area. In most of the cases levels of education were secondary 25

(35.71%) and primary 24 (34.29%), 11(15.71%) were illiterate and higher secondarily were 10(14.29%). Sixteen (22.86%) cases were serviceholder, 15(21.43%) were farmer, 13 (18.57%) were housewife, 12 (17.14%) werestudents, 11 (15.71%) were businessmen and only 3 (4.29%) were rickshawpuller in their occupation. Majority of the cases came from lower 37 (52.86%) and middle 27 (38.57%) socioeconomic condition, 6 (8.57%) cases came from high socioeconomic condition. Fifty per cent of the cases were tobacco users and 50% were not tobacco users. Among the cases 15 (21.43%) presented with nasal polyp and 55(78.57%) cases had no nasal polyp. Most of the cases (64.29%) had no nasal allergy and only 25(35.71%) had nasal allergy. Five (7.14%) cases were in group I (normal IgE); 45.71% (32) cases in group II(moderately raised IgE) and 47.14% (33) had high IgE before MMT (figure-01).

The pre-treatment mean of RSDI and LM scoring of group I: 30.85±9.12 and 0.44±0.05; group II: 41.00±6.00 and 0.75±0.22 and group III: 43.06±13.04 and 1.79±0.44 respectively. The post-treatment mean of RSDI and LM scoring of group I: 13.20±8.56 and 0.54±0.05; group II: 30.70±1.29 and 0.50±0.09 and group III: 39.93±2.94 and 1.71±0.10 respectively.

Among 70 cases, 5 (7.14%) cases were in group I (IgE = ≤25 IU/ml), 32 (45.71%) cases in group II (IgE = >25 to ≤149 IU/ml) and 33 (47.14%) in group III (IgE = ≥150 IU/ml) before MMT.

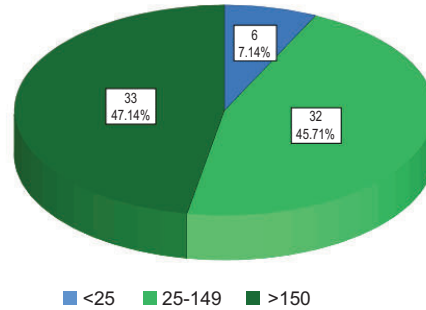


Figure-01: Distribution of study population according to pretreatment serum IgE level (n=70)

This indicated a significantly difference between the two groups, with an estimated mean difference of normal IgE group (group I): -17.65 and 0.10 (95% CI: -20.606 to -14.694 and 0.083 to 0.117 with p-value <0.001***); moderately raised IgE group (group II): -10.30 and -0.25 (95 % CI: -10.605 to -9.995 and -0.306 to -0.194 wit p-value <0.001***); but not significant in high IgE group (group III): -3.13 and -0.08 (95 % CI: -6.2890 to 0.029 and -0.187 to 0.027 with p-value 0.052^{ns} and 0.140^{ns} respectively) (Table-I).

Table-I: Distribution of pre- and post-treatment outcome parameter of the subjects in three groups (n=70) by p value

Parameter	Pre-treatment	Post-treatment	Mean difference	95% CI	p value
Group I: Normal IgE (≤25 IU/ml)					
RSDI	30.85±9.12	13.20±8.56	-17.65	-20.606 to -14.694	<0.001***
LM	0.44±0.05	0.54±0.05	0.10	0.083 to 0.117	<0.001***
Group II: Moderately raised IgE (>25 to ≤149 IU/ml)					
RSDI	41.00±6.00	30.70±1.29	-10.30	-10.605 to -9.995	<0.001***
LM	0.75±0.22	0.50±0.09	-0.25	-0.306 to -0.194	<0.001***
Group III: High IgE (≥150 IU/ml)					
RSDI	43.06±13.04	39.93±2.94	-3.13	-6.2890 to 0.029	0.052 ^{ns}
LM	1.79±0.44	1.71±0.10	-0.08	-0.187 to 0.027	0.140 ^{ns}

Data were expressed as mean ± SD. Paired Student “t” test was performed to compare different pre and post-treatment parameters. Level of significance was calculated at confidence interval of 95% and p value <0.05. n= study subjects, ***=significant.

Discussion:

This study was undertaken to observe the association of pretreatment serum IgE level with the outcomes in patients of chronic rhinosinusitis who got maximal medical therapy, so that IgE can be used as a marker for disease severity. This will help us in taking decision, whether medical treatment is going to be sufficient or should there be the possible need for surgical intervention.

The results of current study demonstrate that majority of the study subjects were young adults and the age range was 18 to 50. In adults, chronic rhinosinusitis caused by the inflammatory response to the presence of bacteria rather than the action of microbes themselves¹⁶. Almost similar findings were observed by the various investigators from different countries¹⁷⁻¹⁸

Both male and female were affected (M: F = 1.3:1). Women have historically been considered more likely to report symptoms, seek medical care, and give poorer self-evaluation of health, which may bias data toward increased prevalence and a greater effect of CRS on quality of life in women¹⁹. However, the influence of gender seems to be restricted primarily to the evaluation of general quality of life, whereas the disease-specific health-related quality of life is not different between genders. Furthermore, migraine headaches, which are more common among women, may be misdiagnosed as CRS, which contributes to gender differences in the prevalence of CRS. The degree to which reported differences in prevalence and health utilization represent biologic or physiologic differences between genders is not known; however, differences in anatomic size, tobacco susceptibility and hormonal factors have been speculated to increase the overall susceptibility to CRS in women compared with men.

Subjects came from rural area, urban area, and slum area. Majorities had primary and secondary level of education and were service holder, farmer, housewife, students, businessmen and rickshaw puller in their occupation. Majorities came from low (52.86%) and middle (38.57%) socioeconomic condition. Poor nutritional status leads to malnutrition, cold, damp, and overcrowded housing responsible for increased risks of infective diseases may be the possible interpretation for this prevalence. A recent study showed factors such as occupation, highest academic qualification, rural/urban location, duration of residency, proximity to crops, annual income, ethnicity, household occupancy and social class were studied in relation to CRS²⁰⁻²¹. No significant association between presence of CRS and these factors were found.

Half of the study subjects in this study were active tobacco users. Disruption of sinus mucociliary action, accumulation of toxic substance due to both active and passive smoking possibly associated with higher rate of CRS. Several studies also reported tobacco as a risk factor for CRS²²⁻²⁵. But conflicting results have been found in previous studies about the effect of smoking on CRS where they found a negative association between smoking and allergic rhinitis²¹. Smoking may have an immunosuppressive effect and reduce the number of IgE sensitizations. But they have found a positive link between smoking and CRS and ARS.

Majority of the subjects were presented without nasal polyp (78.57%) and allergy (64.29%) and only a few cases had CRS with nasal polyp and allergy. These findings were almost similar with study done by Lemos-Rodriguez et al. (2017) where they stratified their study groups according to presence or absence of polyp and nasal allergy. Moderately raised and high IgE groups

contain more subjects with nasal polyp and allergy¹⁵.

Serum IgE level was categorized into Group I: normal IgE (<25 IU/ml), Group II: moderately raised IgE (≥ 25 to <149 IU/ml) and Group III: high IgE (≥ 150 IU/ml). Among them majority of the cases had moderate and high IgE level. Raising of IgE is one of the molecular hallmarks of CRS and our findings were also like that pathophysiology. These findings were similar with previous study.¹⁴

Post-treatment mean RSDI and LM staging were significantly decreased than pre-treatment serum RSDI, and LM staging in group I and group II. In group III, pre- and post-treatment differences were not significant both in QoL and disease severity reduction. In the group III, 45.45% (15) subjects presented with nasal polyposis, 57.58% (19) with nasal allergy and 42.42% (14) presented with both. Medical treatment alone failed to complete reduction of polyp size and mucosal thickening and fibrosis, causing persistent ostial occlusion, leads to MMT failure in this group. Similar findings were observed by Dubin MG et al. (2007), Manohar and Selvakumaran (2012) and Sreenath et al. (2015), but Lemos-Rodriguez et al. (2017) demonstrated that IgE levels did not seem to have a significant effect on the quality of life or outcomes of MMT in the patients with CRS^{11,12,15,26}. However, the presence of nasal allergies regardless of IgE levels seemed to result in more frequent recommendations for surgery after MMT. In the patients with higher-IgE levels (150 IU/ml), MMT seemed to fail at high rates with or without the presence of polyps or allergic disease. This dissimilarity might be due to difference in environmental factors and variation in nutrition.

Conclusions:

The outcome of MMT both in terms of QoL and disease severity was significantly

associated with normal and moderately raised IgE group. There was no significant improvement of QoL and disease severity with MMT in high IgE group. Small sample size, shorter duration of study is a limitation. With large sample size, more stratification with presence of nasal polyp and nasal allergy and a longer follow up period will make the study more fruitful.

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