

Probiotic as supplementary therapy for chronic rhinosinusitis

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Abstract

Chronic Rhinosinusitis is an inflammation in paranasal sinus and nasal cavity that can last up to a minimum of 12 weeks with prevalence 1% to 12% globally. The etiology of chronic rhinosinusitis is usually caused by combination of various factors such as pathogenic organism and obstruction of the sinus tract. The latest study also found imbalance in natural microbiome can cause chronic rhinosinusitis. One of the alternative therapies to help alleviate chronic rhinosinusitis is using probiotic. Probiotic is a living microorganism that, if given in adequate dosage, will provide health benefits for the host by keeping the balance of microbiome or commensal bacteria count in the body. Some latest studies showed the efficacy of probiotic in rhinitis allergy, atopic prevention such as eczema, asthma, diarrhea and food allergy. Aim of this narrative review is to understand the efficacy of probiotic and possible side effects that might occur in the use of probiotics as supplementary therapy on chronic rhinosinusitis.

Keywords: Chronic rhinosinusitis; Probiotic; Microbiome; Immune system; Sinus cavity; Commensal bacteria

1 Introduction

Chronic Rhinosinusitis is a symptomatic inflammation in paranasal sinus and nasal cavity that can occur for minimum 12 weeks. The prevalence of chronic rhinosinusitis varies around the world, ranging from 1% to 12.1% [1]. In the United States, based on 2012 health survey, 1 out of 8 adults suffer chronic rhinosinusitis in the last 12 months.² The prevalence of chronic rhinosinusitis with polyp in Sweden was 2.7% from the entire population, 0.5% in Korea, and 2.1% in France.³ Chronic rhinosinusitis can occur in various race and can greatly impact the medication cost [4]. The total indirect and direct cost of yearly treatment for chronic rhinosinusitis in America is estimated around 22 billion US dollar in 2014, along with additional cost caused by decreased productivity and work effectiveness [2,3].

The etiology of chronic rhinosinusitis is not entirely understood but it might be caused by combination of various factors such as pathogenic organism and obstruction of the sinus tract [5]. The latest study showed that imbalance in natural microbiome can be caused by antibiotic therapy and it may cause chronic rhinosinusitis [6]. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the two most common pathogenic bacteria that causes chronic rhinosinusitis [5].

Due to its uncertain etiology, therapy that is given to alleviate chronic rhinosinusitis is generally symptomatic such as, saline solution irrigation, antihistamine, decongestant and topical or systemic corticosteroid and on some cases an antibiotic is also prescribed if the patient is diagnosed with infection. For some patient, perfect remission is not achieved through the prescription of the previous medication [7]. One of the other possible alternative treatments to alleviate chronic rhinosinusitis is the use of probiotic. Probiotic is a living microorganism that, if given in adequate dosage, will provide health benefits for the host. The purpose of using probiotic is for keeping the balance of microbiome or commensal bacteria counts in the body. Probiotic may help alleviate chronic rhinosinusitis by keeping commensal

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microbiome bacteria in the body, since the imbalance of microbiome is one of the chronic rhinosinusitis' etiology [6,8]. Some latest studies showed the efficacy of probiotic in rhinitis allergy, atopic prevention such as eczema, asthma, diarrhea and food allergy [7,9]. Aim of this review article is to understand the efficacy and possible side effects that might occur in the use of probiotics as supplementary therapy on chronic rhinosinusitis.

2 Chronic rhinosinusitis

2.1 Risk factor and etiology

Chronic rhinosinusitis can be caused by the imbalance between environmental factor and immune system of the host [4]. Environment factors that greatly impact the occurrence of chronic rhinosinusitis including allergen, toxin and microbial agent. Factors from the host may include immunity disorder, both adaptive and mechanic [10]. Microbial agent that commonly caused chronic rhinosinusitis is *Staphylococcus aureus*. Other bacteria may include *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Corynebacterium*, *Acinetobacter spp*, *Proteus mirabilis*, *Enterobacter spp*, and negative-coagulase *Staphylococci*, a bacteria that creates biofilm. The proposed hypothesis regarding to this theory is chronic rhinosinusitis may be caused by the imbalance of microbe. The amounts of pathogenic microbes exceed that of the normal flora that can cause inflammation in the nasal cavity [4]. Latest study showed that colonization of microbiome from commensal bacteria in the sinus, natural microbiome disruption caused by pathogenic bacteria and prolonged antibiotic therapy can cause dysbiosis which later may cause chronic rhinosinusitis [6,11]. High percentage of *S.aureus* was found in chronic rhinosinusitis patient with nasal polyp, but it did not find in chronic rhinosinusitis patient without polyp. Besides *S. aureus*, commonly found bacteria in chronic rhinosinusitis patient are negative-coagulase *Staphylococcus*, and *Pseudomonas aeruginosa*. Lal et al conducted study that compared microbiota that found on meatus media and inferior on chronic rhinosinusitis patient with or without polyp and a healthy subject. The study found that large number of *Streptococcus*, *Haemophilus* and *Fusobacterium spp* is prevalent in chronic rhinosinusitis patient compared to the healthy subject [12].

2.2 Microbiome

Various microbes and its genome found in certain organs can be defined as microbiome. There are around ten trillion to 100 trillion microorganisms found in human body, this number exceeds the amount of the human cell. Those Microorganism can live in various surfaces which contact with the environment such as skin, gastrointestinal and respiratory tract. Microbiome plays an important role in keeping health as well as the growth of disease in human. Imbalance in microbial count (dysbiosis) can potentially cause inflammation in certain areas that includes digestive tract, allergy and obesity. Other study showed that dysbiosis is related with chronic rhinosinusitis. The connection between chronic rhinosinusitis and nasal microbiome was studied to determine the microorganism that might cause chronic rhinosinusitis. The result of the observation showed that there were no specific microbes pattern in chronic rhinosinusitis patient. Study also showed that dysbiosis or lack of biodiversity in species of bacteria plays an important role in the severity of chronic rhinosinusitis [8].

One of the bacteria that can potentially cause chronic rhinosinusitis is *Staphylococcus Aureus*. *S. Aureus* is a gram-positive bacteria which can be pathogenic or commensal. Colonization of *S. Aureus* in the nasal cavity and sinus is related with the nasal polyp or the severity of the disease. Other pathogen which can be found on nasal cavity or sinus of chronic rhinosinusitis patient is *Pseudomonas aeruginosa* [8]. In study that involved 59 Chronic Rhinosinusitis patients, found colonies of *Streptococcaceae*, *Pseudomonadaceae*, *Corynebacteriaceae*, and *Staphylococcaceae*. Through bacterial culture observation on swab middle meatus specimen from 165 Chronic Rhinosinusitis patients with nasal polyp, 76 Chronic Rhinosinusitis patients without polyp and 44 control subject, Liu found coagulase-negative *Staphylococcus* on three group subject while *S. aureus*, *Streptococcus*, *Haemophilus*, *Enterobacter*, dan *Corynebacterium* are found on patient with nasal polyp [4].

2.3 Standard Therapy for Chronic Rhinosinusitis

Exacerbation of Chronic Rhinosinusitis is caused by unfinished treatment. It can re-occur periodically, mainly caused by *S. aureus*, anaerobic bacteria, and gram-negative rods and usually need antibiotic treatment. Antibiotics used are mainly empiric and narrow spectrum if the cultured are available. Empiric antibiotic for chronic rhinosinusitis treatment must target the bacteria which are commonly found such as *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *P. aeruginosa* and anaerobic bacteria. Chronic rhinosinusitis with nasal polyp occurs due to bacterial colonization, such as *staphylococcus*, which produces SAG that in turn increases inflammation which is mediated through eosinophil thus creating nasal polyp. Chronic rhinosinusitis with nasal polyp (CRSwNP) can be treated with intranasal steroid and/or saline irrigation to reduce clinical symptom, prolonged treatment of intranasal glucocorticoid is given to reduce the size of the polyp, recurrence and reducing the symptom of chronic rhinosinusitis and to fix the air

flow in the nasal cavity. Oral intake of corticosteroid can also reduce the size of the polyp, but can only be administered on a short term due to its side effects. Antibiotic administration from the macrolida group can also be considered for its anti-inflammatory effect. On chronic rhinosinusitis patient without nasal polyp (CRSsNP), intranasal steroid therapy and/or saline irrigation will benefit in reducing the clinical symptom. Topical antibiotic will not benefit for patient with CRSsNP. Oral antibiotic in the long term, especially macrolide (Azithromycin 500g per week or roxithromycin 150g per day) shows response after 12 weeks therapy. Prolonged antibiotic use with low dosage will result in resistance and prolonged infection [4].

3 Probiotic

WHO define probiotic as living microorganism that if given on an adequate dosage can give health benefits to its host [10]. Probiotic is generally a commensal bacteria, though some may not be commensal bacteria such as *Lactic acid bacteria* (LAB), species of *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, dan *Enterococcus*. Probiotic must be safe to be consumed, can survive in the digestive tract, can adhere to the digestive tract mucosa, create antimicrobial substance, can antagonize pathogenic bacteria, can form a colony in the intestine and is stable during production and storage. Probiotic can increase immunity directly and through competition with pathogenic bacteria or indirectly modulate humoral immunity and natural immunity of the host [13]. Some studies have already found the effect of probiotics in various indications, both related and not related to the gastrointestinal tract.

Studies found that *Lactobacillus rhamnosus* GG 1×10^{10} dosage colony forming units (cfu)/day is effective to treat eczema and atopic dermatitis in babies and children.¹³ Other studies also shown that short term administration of *Bifidobacterium longum* 2×10^{11} dosage cfu/day and 6 g prebiotic fructo-oligosacharides is effective to treat colitis ulcerativa. *Bifidobacterium* will compete with the microorganism that is responsible as etiology or directly impact the cytokine in expressing the inflammation [14]. Administration of *Lactobacillus* GG 7.1×10^9 cfu/day, *Streptococcus thermophilus* 27×10^9 cfu/day, *Lactobacillus acidophilus* 3.2×10^9 cfu/day, and *Bifidobacterium* sp 8.4×10^9 cfu/day can significantly decrease the pathogenic bacteria in the respiratory tract on healthy subject [11]. Beside the benefit, according to WHO and Food And Agriculture Organization of the United Nation in 2002, probiotic can possibly cause a systemic inflammation, change in metabolic activity, overstimulation of immunity in susceptible individuals and cause some side effects on digestive tract [15].

3.1 Probiotic and Immune System

Probiotic can be consumed in form of fermented food/drinks (ex: cheese, yoghurt) and is generally uses bacteria from species Lactobacilli and/or Bifidobacterium. These bacteria are anaerobic bacteria and can ferment food into lactic acid in the gastrointestinal tract, making it possible to dominate and defeat pathogenic microorganisms in the digestive tract [16]. Probiotic has function as indirect immunomodulators through the interaction between probiotics and the host immune system, which are:

- Humoral immunity by stimulating Th 1, and suppressing Th 2, stimulation of *transforming growth factor* β (TGF- β), and increase the production of IgA which will affect the mucosal defense.
- Innate immunity/adjuvant effects: *toll-like receptor* (TLR-2) signal, *nucleotide-binding oligomerization domain receptors* (NODs) signal or lectin signal and interaction with *dendritic cells* (DC) which will modulate the maturity of DC and its cytokine.

The concept of mucosal immunity generally states that activated lymphocyte can migrate from one mucosal in certain organ to other mucosal in another organ. Mesenteric lymph gland plays an important role in mucosal immunity especially in inducing intestine mucosal immunity and systemic immunity. Commensal bacteria or probiotic bacteria can enter the mesenteric lymph gland through intestinal dendritic, but not the thorax lymph gland, and enter the systemic circulation. Therefore, microbes that is related with dendritic cells in mesenteric lymph gland will impact the systematic immunity, mainly the growth of T cell and B cell in systemic circulation [17].

Gut-associated lymphoid tissue (GALT) is the largest lymphoid tissue in a human body. GALT is the first tissue exposed to microbes and is the largest colonization of microbes in the intestine. Colonisation of this commensal bacteria is important in stimulating the growth of an immune balance, making it function optimally, not just as mediator for T cell and B cell into lamina propria and expansion and maturation of IgA plasmocytes and production of IgA. Colonization of this commensal bacteria also can induce tolerance for antigen microbes [18].

3.2 Probiotic and Chronic Rhinosinusitis

Some probiotic studies have been conducted for allergy and chronic rhinosinusitis. In those studies, probiotic is administered orally with low success rate, hence other studies focused on administering topical probiotic through nasal spray. Preclinical study was conducted by Lynch, reported that administration of *Lactobacillus kasei* can inhibit the growth of pathogenic bacteria *Corynebacterium tuberculostereaticum* [19]. Study by Martensson, in 2017 on 21 chronic rhinosinusitis patients with polyp were administered with nasal spray that consists of 40 million (10^6) CFU LAB (combination of 9 *lactobacillus* and 4 *bifidobacteria*) were then compared with a nasal spray that consists of only placebo for 14 days. This study shown that there were no significant differences between the treated and control group which was evaluated through SNOT-22, microbiology examination and inflammation mediator in the nasal area [6]. Further study was conducted by Alromaih S in 2016, that used topical probiotic that contains 1.2 million CFU *Lactococcus* lactic W136 twice a day for 14 days on patients with chronic rhinosinusitis with or without nasal polyp. That study found that 24 patients which received the therapy showed improvements on clinical symptoms, life quality score and endoscopy score. Other than that, the expressed gen profile shown improvements in epitel cell regeneration and further microbiome examination using 16 s technology shown the reduction of pathogenic bacteria *Staphylococcus aureus*, *Peptostreptococcus*, dan *Enterobacteriaceae* [19]. Other study by Mukerij in 2009, was conducted to 77 chronic rhinosinusitis patients administered *Lactobacillus rhamnosus R0011* twice a day for 4 weeks compared to placebo.⁷ On that study, there were no significant differences found between the treated and control group which were evaluated with SNOT-20 and clinical symptoms of the patient.

4 Conclusion

Microbiome imbalance is one of etiology of chronic rhinosinusitis. In this situation, the abnormal number of microbes and more pathogens can cause inflammation on sinus cavity, causing chronic rhinosinusitis. Several studies have shown that probiotics can ferment food into lactic acid, making it possible to defeat pathogenic microorganisms so it can reduce colonization of pathogenic bacteria. In addition, probiotics also can modulate the host's immune system. Several preclinical studies have proven that the use of probiotics can inhibit the development of pathogenic bacteria. Several clinical trials of probiotics in patients with chronic rhinosinusitis have also shown an improvement in clinical symptoms in patients receiving probiotics. However, further clinical trial needs to be done with a larger number of subjects to prove the probiotic's efficacy.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest in this study.

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