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Review Article

Topical Management of chronic rhinosinusitis - A literature review

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Introduction

Chronic rhinosinusitis (CRS) is an inflammatory condition involving nasal passages and the paranasal sinuses for 12 weeks or longer [1]. It can be subdivided into three types: CRS with nasal polyposis (CRS with NP), CRS without nasal polyposis (CRS without NP), and Allergic fungal rhinosinusitis (AFRS). To diagnose CRS we require at least two of four of its cardinal signs/symptoms (nasal obstruction, mucopurulent discharge, facial pain/pressure, and decreased sense of smell). In addition, direct visualization or imaging for objective documentation of mucosal inflammation is required. CRS therapy is aimed to reduce its symptoms and improve quality of life as it cannot be cured in most patients. Thus, the goals of its therapy include the following:

1: Control mucosal edema and inflammation of nasal and paranasal sinuses

2: Maintain adequate sinus ventilation and drainage

3: Treat any infecting or colonizing micro-organisms, if present

4: Reduce the number of acute exacerbations

Mucosal remodeling is the most likely underlying mechanism causing irreversible chronic sinus disease, similar to that occur in severe asthma. In patients with both disorders, medical treatment of CRS can help in asthma control [2]. Multiple topical and systemic therapies are used in the management of CRS, including saline washes and sprays, intranasal and systemic glucocorticoids, anti-leukotriene agents, and antibiotics. Recently, several systematic reviews evaluated the most commonly used therapies and stressing the need for more research as evidence supporting most of them was of low quality [3-5]. We did a systemic search to overview local therapies used in the management of CRS.

Topical therapies for chronic rhinosinusitis

Nasal Saline: Saline irrigations are used to freshly clean the nasal mucosa as irrigating the nasal cavities with saline removes secretions, decreases postnasal drainage, and washes away allergens and irritants. It can be used shortly prior to administering other intranasal medications. Based on clinical impression and limited data it is suggested that saline nasal irrigation is more effective in preference to using saline nasal sprays [6,7]. A Cochrane analysis suggested that compared with placebo it is more helpful to use daily large volume saline irrigation with a hypertonic (2%) saline [8]. It can be used with multiple devices including syringes, squeeze bottles, and pots. These saline solutions are not only made commercially but patients can also make their own. Depending on the severity of symptoms, nasal lavage (with at least 200mL warmed saline in each nostril) can be used with variable frequency (as needed only, once daily, or multiple times daily). Careful reviews of studies involving the use of

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saline sprays and irrigation found that monotherapy with nasal saline is less effective than adjunctive treatment for CRS [8,9]. Periodic microwaving of irrigation bottles should be done to ensure that bottles do not become contaminated [10].

Surfactants: Surfactants are a category of compounds which demonstrate amphipathic properties, containing both hydrophobic and hydrophilic characteristics that allow the compound to be solvent in both water and organic substrates. The rationale for surfactant use is the fact that it has two potential benefits, as a biocide with activity against planktonic and biofilm-associated microbes as well as being a mucoactive agent which decreases the mucus viscosity.

The surfactants, such as baby shampoo, are believed to prevent the bacterial biofilms formation on the sinus mucosa and increase mucociliary clearance. A study was done to analyze the effects of baby shampoo (1% solution) in physiologic saline in 18 postsurgical patients, with twice daily sinus irrigations for four weeks [11]. 11 of those patients reported subjective thinning of mucus and improvement in postnasal drainage. However, there was no objective measurement of mucosal disease or biofilm. Based on the above findings and in vitro studies [12], it is warranted to further study the role of surfactants in the management of CRS. The author of the study found that nasal rinses combined with a surfactant may be effective in patients with recurrent acute rhinosinusitis in decreasing the number of symptomatic episodes.

Topical Steroid: Nasal Irrigation can be done by adding budesonide to saline or budesonide as an aqueous nasal spray have been found effective in treating chronic rhinosinusitis. The theory behind budesonide use in irrigation is that higher concentrations of steroids can be topically delivered to sinus mucosa than what is available as a nasal steroid spray.

We have the following recommendations to optimize the effectiveness of nasal sprays and improve patient compliance:

1: It is convenient for patients to use preparations with once-daily dosing with improved compliance. These preparations include fluticasone propionate, fluticasone furoate, budesonide, triamcinolone acetonide, and mometasone furoate. Most of these agents are used once or twice daily with one to two sprays in each nostril.

2: In case of obvious mucus or crusting, the nose should be cleaned with nasal saline sprays or irrigation before applying the nasal glucocorticoid sprays.

3: Position of the head while spraying should be slightly downward as tilting the head back can cause spillage of the medication to the throat. Additionally, the tip of the bottle should be directed laterally in the nostrils to minimize nasal septum irritation and bleeding.

Glucocorticoid solutions in the form of drops or nebulizing solution can reach the middle meatus more reliably than nasal sprays [13]. Glucocorticoid solution of fluticasone propionate and betamethasone are commercially available as nasal drops in the United Kingdom and Europe. In the United States, glucocorticoid solution of budesonide in the form of nebulization is available and can be used in the following form. The “concentrated rinse” of budesonide is usually prepared by combining its one respule (0.5mg in 2mL) with 5 mL of saline solution making a mixture with budesonide concentration of 71.4 micrograms/mL. Lesser concentrations can also be made by mixing half respule depending on what is believed most suitable for the patient. A syringe with a specialized nasal tip is mostly used to instill the concentrated budesonide rinse.

A small number of studies to evaluate the efficacy of glucocorticoid instillations have been done. In a study involving 54 patients with CRS with or without nasal polyps

having a refractory disease, the efficacy of fluticasone propionate nasal drops was demonstrated [14]. For three months, patients were treated with either fluticasone propionate or placebo. Compared to placebo, the patients treated with fluticasone had clinically significantly more improvement in symptoms, nasal airflow, and polyp volume.

The long-term safety has not been established for different glucocorticoid nasal instillations, although it is known that a very small amount of the instilled solution is retained [15]. Another study involving nine patients treated with budesonide solution for 30 days shown significant clinical improvement in CRS [16].

Nasal nebulized solutions of glucocorticoid are also available and can be administered as 0.5mg in each nostril daily. The nebulized solutions are effective in patients unable to perform nasal instillation due to problems with the technique. The efficacy and safety of nebulized solutions were evaluated in a randomized trial involving 60 patients having eosinophilic CRS with Nasal Polyps, treated with either a budesonide solution or placebo for two weeks [17]. The results showed significant clinical improvement in the symptoms and size of the polyp. Morning plasma cortisol was measured at the end of the study to evaluate for adrenal suppression, but there was no evidence of it. It is noteworthy that this study used a higher dose of budesonide solution(1 mg in each nostril daily). However, it was not proposed to use this higher dose of nasal nebulization for chronic use.

Antibiotics: The role of both topical and systemic antimicrobials in CRS has been re-examined as CRS pathophysiology involves complex inflammatory changes instead of persistent bacterial infection. Evidence in the support of antimicrobials as monotherapy is of low quality and limited [3]. The main goal of managing CRS is to control the inflammation that predisposes to obstruction, ultimately minimizing the chances of infections. Despite this, patients with CRS are prone to secondary bacterial infections secondary to poor sinus drainage requiring antibiotics. Whenever feasible, purulent mucus should be obtained from middle meatus or another sinus ostium endoscopically for culture, which should determine the choice of appropriate antibiotic [18-20]. Nasal swabs shouldn't be used for culture as they don't have sinus contents. If endoscopy is not feasible antimicrobial agents should be chosen empirically except in following clinical settings:

- Failed antibiotic treatment with a similar regimen in recent past
- History of infection with methicillin-resistant Staphylococcus aureus(MRSA) or gram-negative or another highly drug-resistant bacteria
- The patient is highly immunocompromised with increased risk for invasive fungal rhinosinusitis

Such patients should undergo nasal endoscopy to obtain culture material.

Antifungal (Oral or intranasal): Allergic fungal rhinosinusitis (AFRS), a form of CRS involves fungal colonization. Both systemic and topical antifungals (either amphotericin B or itraconazole) have been studied in AFRS in some of the clinical trials, with mostly unfavorable results [21,22]. A meta-analysis and a systematic review, involving antifungal therapy found no statistically significant advantage of systemic or intranasal antifungals over placebo, and higher adverse events rates in patients with antifungal groups [23,24]. The literature has revealed a lot of controversies in CRS etiology with regards to fungus. Ponikau and coworkers [25], hypothesized that colonization by fungus plays a major stimulus for persistent inflammation in patients with CRS, including those with or without nasal polyp.

Although there has been a lot of initial enthusiasm for the use of topical antifungal

agents, several subsequent studies have not been able to prove its superior benefits over saline irrigation [26,27]. Also, a multicenter high-dose double-blind study of terbinafine (Lamisil) in the treatment of CRS Carried out by Kennedy and colleagues [28], have not proved any significant in relation to symptomatic or radiographic resolution.

Oral antifungal agents have been proposed as an effective treatment option for selected patients with allergic fungal sinusitis [29,30], (AFS) and nonallergic eosinophilic fungal sinusitis [31], diseases. Also, Topical antifungal therapy has been reported in a study in one out of five trials to be effective [32], for radiographic and endoscopic scores, but not for symptoms. Three trials used nasal irrigation [32,33] and two trials used nasal sprays [34,35], in administering the antifungal agent or placebo.

Nasal drops were found to clear more quickly from the nose than nasal sprays [36,37].

Fluticasone propionate is a potent, topically active corticosteroid, available as either an aqueous nasal spray or aqueous nasal drop preparation in a single dose. The drops preparation deliver more of the drug to the affected sinus mucosa [36]. Both nasal spray and nasal drop preparations were shown to exhibit a low systemic bioavailability, but the bioavailability of nasal drops was approximately eight times lower (0.06% vs 0.51%) [38].

Conclusion

Topical therapies are usually the first line of treatment in most case of chronic rhinosinusitis (CRS). Most of the patients with CRS cannot be cured, and the goal of therapy is to provide symptomatic relief and improve quality of life.

Multiple topical and systemic therapies are employed in the management of CRS, including intranasal saline, surfactants, glucocorticoids (intranasal and systemic), antibiotics, and antifungal agents. These medications are combined in various ways to manage CRS depending on the subtype and severity of clinical presentation.

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