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Rhinitis Medicamentosa Caused by Imidazoline Topical Decongestants: Literature Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Aims: The aim of the study is to systematize available scientific data on rhinitis medicamentosa caused by imidazoline topical decongestants.
Materials and Methods: To meet the aim of the study, publications from open scientific databases accessible via the Internet were reviewed based on the following search terms: "rhinitis medicamentosa", "rebound congestion", "imidazoline", and "topical decongestants".
Results: Rhinitis medicamentosa holds one of the leading positions among chronic non-allergic rhinitis, primarily characterized by nasal congestion. Ineffective examination and treatment of patients with allergic and non-allergic rhinitis, anatomic anomalies of the nasal cavity, and wide accessibility of nasal decongestants in pharmacies have contributed to a significant spread of this problem. Rhinitis medicamentosa typically occurs after prolonged (>5 days) use of topical decongestants. Imidazoline decongestants act as α-agonists, causing constriction of blood vessels; their prolonged use can result in mucous membrane swelling and tachyphylaxis. The main histopathological changes associated with rhinitis medicamentosa include epithelial destruction, nerve-ending degeneration, edema, and fibrosis. Rhinitis medicamentosa is rather difficult to treat, and the outcome is not always satisfactory.
Conclusions: Because of the difficulty and lack of efficacy of treatment for rhinitis medicamentosa,

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new ways of prevention are brought to the fore. Prevention of this pathological condition by combining imidazoline topical decongestants with other groups of topical drugs is one of the possible ways to solve this problem.

Keywords: Rhinitis medicamentosa; rebound congestion; imidazoline; topical decongestants.

1. INTRODUCTION

Nasal congestion severely affects quality of life, social activities, sleep, school/workplace performance, and the ability to perform daily activities. Based on expert estimates, the prevalence of nasal congestion in the population is 30% [1]. Topical nasal decongestants are frequently used in patients with acute rhinitis, rhinosinusitis, and rhinopharyngitis. They have proven effective, but quick relief of nasal congestion and their accessibility may often contribute to uncontrolled drug use and excessive self-medication.

“Rhinitis medicamentosa, also called rebound congestion or chemical rhinitis, is a drug-induced, chronic, non-allergic form of rhinitis that is a chronic dysfunction of the nasal mucosa due to prolonged use of local vasoconstrictors” [2,3]. “Drug-induced rhinitis is a type of non-allergic rhinitis caused by several medications, including angiotensin-converting enzyme inhibitors, reserpine, guanethidine, phentolamine, methyldopamine, prazosin, beta-blockers, chlorpromazine, aspirin, other nonsteroidal anti-inflammatory drugs, and oral contraceptives” [4,5,6]. Some authors point to the differences between the mechanisms by which topical decongestants and oral medications cause nasal congestion. That is why several authors distinguish the term rhinitis medicamentosa among all types of drug-induced rhinitis.

“The overuse effects of topical decongestants were described for the first time by Fox in 1931” [7]. Feinberg et al. [8] used the term “rebound congestion” in 1945 to describe a clinical case where a patient experienced nasal congestion after using naphazoline hydrochloride. “In 1946, Lake introduced the term rhinitis medicamentosa” [9]. “The first diagnostic criteria for rhinitis medicamentosa were proposed in 1952 and included the history of prolonged use of nasal decongestants, constant nasal obstruction, and distinct shrinkage of the nasal mucosa during examination” [10].

The aim of the study is to systematize available scientific data on rhinitis medicamentosa caused by imidazoline topical decongestants.

2. MATERIALS AND METHODS

To meet the aim of the study, publications from open scientific databases accessible via the Internet were reviewed based on the following search terms: “rhinitis medicamentosa”, “rebound congestion”, “imidazoline”, and “topical decongestants”.

3. RESULTS AND DISCUSSION

“Rhinitis medicamentosa is usually characterized by nasal congestion without rhinorrhea, postnasal drip, or sneezing that begins after using nasal decongestants for more than five days” [3,11,12]. “Such medications are used to relieve nasal congestion in patients with allergic rhinitis, non-allergic rhinitis, acute or chronic sinusitis, nasal polyposis, pregnancy rhinitis, or rhinitis due to nasal septal deviation” [13]. They are also often used by individuals with viral upper respiratory tract infections, 25% to 50% of whom may develop rhinitis medicamentosa [3].

“Rhinitis medicamentosa occurs with equal frequency in men and women but is more common in young and middle-aged adults” [2,14]. “The incidence of rhinitis medicamentosa reported in otolaryngology clinics ranges from 1% to 7%” [15]. “Besides, out of 500 patients with nasal congestion in an allergy clinic, 9% had rhinitis medicamentosa” [3,16].

“The pathophysiology of rhinitis medicamentosa is still unclear. However, it is known that the nasal mucosa consists of resistance and capacitance blood vessels. Resistance blood vessels, including small arteries, arterioles, and arteriovenous anastomosis, drain into the capacitance vessels, which are composed of venous sinusoids” [17,18]. “The venous sinusoids are innervated with sympathetic fibers, and when stimulated, these nerves release noradrenaline, which binds to α1- and α2-receptors. This leads to reduced nasal congestion by decreasing blood flow and increasing sinus emptying in the capacitance vessels” [19,20]. “Other nerves, such as parasympathetic, sensory C-fibers, and non-adrenergic, non-cholinergic peptidergic nerves,

also contribute to nasal congestion" [21]. "Local inflammatory mediators also affect nasal congestion by inducing changes in nasal resistance and capacitance vessels. Mast cells, eosinophils, and basophils contribute to nasal congestion through the release of histamine, tryptase, kinins, prostaglandins, and leukotrienes" [18].

Nowadays, there are two different hypotheses related to rhinitis medicamentosa pathogenic mechanism. The first hypothesis is associated with the long-term and frequent use of alpha-adrenergic agonists, leading to a decrease in the production of endogenous noradrenaline. The second hypothesis states that a decrease in the sensitivity of vascular smooth muscles to endogenous noradrenaline is observed in patients, resulting in an increase in blood volume in the cavernous vasculature of nasal turbinates and, subsequently, swelling of the nasal mucosa. The first mechanism is reversible and observed in healthy patients; the second mechanism contributes to drug-induced dependence in patients with nasal hyperreactivity. Reduced blood flow in the nasal mucosa is associated with hypoxia and possible negative neural feedback. The rebound syndrome has developed. It is demonstrated by a decreased sensitivity of receptors to endogenous noradrenaline and nasal decongestants, leading to a requirement for higher doses of decongestants, whose further use results in dryness, burning, an increased risk of nosebleeds, and a decrease in nasal barrier functions [2,22,11].

As rhinitis medicamentosa is primarily caused by prolonged use of imidazoline nasal decongestants, it is necessary to dwell on details of the mechanisms of their action.

"Nasal imidazolines include oxymetazoline, naphazoline, xylometazoline, and clonidine" [23,24]. "Sympathomimetic amines mimic the actions of the sympathetic nervous system through the presynaptic release of norepinephrine in sympathetic nerves. Norepinephrine then binds postsynaptically to α-receptors and results in vasoconstriction. They are also mild ß-receptor agonists and cause rebound vasodilation without affecting blood flow" [25]. The imidazolines are primarily α2-agonists that act postsynaptically on sympathetic nerves and cause vasoconstriction. They also lower the production of endogenous noradrenaline via a negative feedback mechanism, thus decreasing blood flow and decongesting the nose. In the study by Cauna et al. [26], "plasma cells were found surrounding degenerating autonomic and sensory nerve endings in the nasal mucosa". "In rabbits after the administration of either oxymetazoline or phenylephrine, acute purulent maxillary sinusitis developed in 13,3% of the first group and in 33,3% of the second group, which additionally describes the side effects of this category of drugs" [27].

In another study, rabbits received two (2) intranasal puffs of xylometazoline 0,5 mg/mL twice daily [28]. The following histologic changes were observed after two weeks: inflammatory cell infiltration, edema, congestion, degeneration of nerve endings and epithelium.

Loss of epithelium cilia and decreased goblet cell numbers were observed following administration of 0,05% oxymetazoline to rats for 9 days [29].

In general, rhinitis medicamentosa is associated with the following pathological changes:

1) nasociliary loss and changes in the nasociliary structure;
2) squamous cell metaplasia;
3) increased mucus production;
4) epithelial cells change from ciliated columnar to nonciliated, stratified squamous;
5) epithelial cell denudation;
6) increase in intercellular widening, vascularity, fibrosis, and edema of the epithelial cell layer;
7) goblet cell hyperplasia;
8) increase in epidermal growth factor receptors in the epithelial cell layer;
9) increase in lymphocytes, fibroblasts, and plasma cells.

Based on the available information, rhinitis medicamentosa develops after 3 days of treatment with xylometazoline [11]. However, clinical trials of prolonged use of xylometazoline demonstrated mixed results.

The use of xylometazoline three times daily for 6 weeks in healthy volunteers did not provoke any major functional or structural changes in the nasal mucosa when using electron microscopy [30].

Total nasal resistance was measured by anterior rhinomanometry before and after three weeks of treatment with xylometazoline in the nasal form [13]. Total nasal resistance at rest was

significantly higher in the group of patients with vasomotor rhinitis than in the control group on the initial measurement. The difference increased after the treatment period, but tolerance to xylometazoline did not develop. The study showed that following xylometazoline use, rhinitis medicamentosa developed in predisposed individuals, and interstitial edema of the nasal mucosa was a possible contributing pathophysiological mechanism.

Either a 10-day [31] or 4-week [32] study of oxymetazoline did not demonstrate the development of rhinitis medicamentosa.

At the same time, based on the results of another 4-week oxymetazoline study in health volunteers [33], rhinitis medicamentosa did not develop after 10 days. However, it was registered in all subjects after 30 days.

It is important not only to understand pathological processes in the nasal mucosa but also to diagnose rhinitis medicamentosa.

The main diagnostic criteria for rhinitis medicamentosa, besides nasal obstruction (hyperemia, nasal mucosal swelling with impaired nasal breathing, and nasal congestion) and reduction in the swelling of the nasal mucosa following the administration of vasoconstrictors, are prolonged use of nasal decongestants in patient history. The following aspects are specific to rhinitis medicamentosa [3,5,6,8,27]:

- constant nasal obstruction, dryness, itching, and nosebleeds; nasal intonation of the voice; and a reduced sense of smell can be developed;
- discharge, sneezing, and nasal itching are, as a rule, not typical;
- constant nasal obstruction severely affects nasal breathing, quality of life, sleep, social activities, and cognitive functions;
- nasal mucosa is bright red under rhinoscopic visualization;
- specific tachyphylaxis in response to nasal decongestants is quickly reduced with repeated use over 5-7 days, leading to their overuse;
- patients quickly recover after withdrawal from decongestants; the most difficult period after the withdrawal is the first 7 days;
- positive effect of intranasal glucocorticosteroids, saline solutions, antihistamines, and, in severe cases, systemic glucocorticosteroids;
- rhinitis medicamentosa can be accompanied by allergic rhinitis or other types of non-allergic rhinitis.

There are currently proven treatment options for patients with rhinitis medicamentosa. The first goal in the treatment of rhinitis medicamentosa is the abrupt cessation of nasal decongestants. It has been suggested earlier that a nasal decongestant should continue to be used in one nostril as much as needed until the congestion is relieved in the opposite nostril [14]. However, this practice has never been confirmed in a randomized clinical trial. Immediate discontinuation of a nasal decongestant can cause rebound swelling and congestion. There are several treatments to solve this therapeutic problem, such as nasal cromolyns, sedatives, and saline nasal sprays, but any prospective trials specifically for this form of rhinitis have not been conducted. At the same time, it is essential to explain to a patient that discontinuation of nasal decongestants may worsen nasal congestion, and it cannot be interpreted as an inappropriate treatment strategy. Persistence of a physician and motivation of a patient are essential conditions for successful therapy of rhinitis medicamentosa.

Some studies have demonstrated the positive effects of corticosteroid injections. Thus, Mabri R.L. [34] recommended injecting triamcinolone acetonide 20 mg into the anterior nasal turbinates to reduce interstitial edema in rhinitis medicamentosa, but no clinical trials or case reports were provided to support this recommendation. Mowat G.G. [35] reported “a decrease in nasal congestion in 3 subjects with rhinitis medicamentosa after injecting 2 mL of 2,5% (25 mg/mL) prednisolone solution into the inferior nasal turbinates. Despite these reports, injected corticosteroids are not recommended for routine treatment of RM because of the inherent risks of administering them into the nasal cavity and the discomfort associated with their administration. No randomized controlled trials are available to prove the beneficial effects of corticosteroid injections, oral corticosteroids, or oral antihistamines”.

Intranasal corticosteroids are the only drugs whose efficacy in rhinitis medicamentosa has been proven not only in experimental but also in randomized placebo-controlled clinical trials. Intranasal corticosteroids are currently considered the most effective drugs available for the treatment of patients with rhinitis medicamentosa [2,6,22,36,37]. Topical

corticosteroids are used to alleviate the symptoms of rhinitis, especially during the withdrawal of nasal decongestants, because they are the most effective drugs to relieve reactive congestion after decongestant withdrawal.

The efficacy of intranasal corticosteroids is associated with their local action, as their oral administration in similar doses does not produce the desired effect [38]. Modern intranasal corticosteroids are safe if prescribed at recommended doses for a long period of time. The intranasal route of administration ensures effective local concentration of a corticosteroid with a minimal risk of systemic adverse effects as topical corticosteroids transform into low-active metabolites when they reach the systemic circulation. However, it is important to remember that nasal congestion in patients with presumed rhinitis medicamentosa may not only be caused by a nasal decongestant but may instead be worsened by a concomitant condition such as allergic rhinitis, non-allergic rhinitis, or other nasal pathology [39].

4. CONCLUSION

Rhinitis medicamentosa holds one of the leading positions among chronic non-allergic rhinitis, primarily characterized by nasal congestion. Ineffective examination and treatment of patients with allergic and non-allergic rhinitis, anatomic anomalies of the nasal cavity, and wide accessibility of nasal decongestants in pharmacies have contributed to a significant spread of this problem, making further trials essential.

Because of the difficulty and lack of efficacy of treatment for rhinitis medicamentosa, new ways of prevention are brought to the fore. Prevention of this pathological condition by combining imidazoline topical decongestants with other groups of topical drugs is one of the possible ways to solve this problem.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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