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Intranasal Capsaicin Treatment for Non Allergic Rhinitis

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Mini Review

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Abstract

The diagnosis of nonallergic rhinitis, a type of chronic rhinitis, is made by excluding allergic and infectious rhinitis. There is currently no specific method used in diagnosis. It has been determined that rhinitis symptoms occur in nonallergic rhinitis through neuromediators secreted from the TRPV1 receptor located in the nerve endings of sensor c fibers in the nasal mucosa. The initial effect of capsaicin, which acts in this way, is stimulation, while repeated doses are desensitization. Thus, with repeated doses, capsaicin provides control of non-allergic rhinitis symptoms during a long refractory period (lasting several months). Among the reasons why it has not yet come into widespread use are that it causes burning in the nasal mucosa in the first doses, excessive secretion and low comfort, and the minimum effective dose has not yet been clearly determined. In order for capsaicin to become widespread in the treatment of non-allergic rhinitis, studies are needed to determine its effectiveness with low side effects.

Keywords: Intranasal Capsaicin; Treatment; Nonallergic Rhinitis; Patients; Sphenopalatine Ganglion

Abbreviations: AR: Allergic Rhinitis; NAR: Non-Allergic Rhinitis; NANIPER: Non-Allergic Non-Infectious Perennial Rhinitis; IR: Idiopathic Rhinitis; MPO: Myeloperoxidase; NO: Nitric Oxide; VAS: Visual Analogue Scale; TSS: Total Symptom Score; TRE: Treatment Response Evaluation; ISS: Participant Symptom Score; TNSS: Total Nasal Symptom Score.

Introduction

Chronic rhinitis is a condition characterized by nasal congestion and obstruction, rhinorrhea, itching, sneezing and postnasal drip, which develops as a result of chronic inflammation of the nasal mucosa [1,2]. The rate of rhinitis has been reported as 10-40% of the population in the industrial countries [3].

Allergic rhinitis (AR) is characterized by allergen-induced IgE-mediated inflammation. Non-allergic rhinitis (NAR) is a group of diseases characterized by activation of rhinitis symptoms by triggers without any inflammation. It has been emphasized many times that there are no pathognomonic symptoms for AR and NAR, as their symptoms are similar.

We see that non-allergic and allergic rhinitis components coexist in a group of patients, and these are classified as mixed type rhinitis [4]. In these patients, in addition to the symptoms of perennial allergic rhinitis throughout the year, symptoms and signs consistent with seasonal allergic rhinitis are present [5]. It has been reported in the Cochrane database that NAR is seen in approximately 25-50% of total rhinitis cases [6].

There is currently no specific diagnostic test for the diagnosis of NAR. Therefore, the diagnosis of NAR is actually a diagnosis of exclusion. In order to make this diagnosis, specific IgE in the blood and skin test as well as local IgE in the nose must be negative. In addition, in order to be diagnosed with NAR, there should be no inflammatory and infectious pathology and there should be no anatomical pathology such as septal deviation, polyp, osteomeatal complex obstruction [7]. In addition, the symptoms are frequently triggered by irritants such as smoking, perfume, odour, temperature and humidity changes, but it is not characteristic of all NAR patients to develop a response to all of these triggers [8].

NAR is divided into subgroups according to etiological characteristics. There is no consensus yet on the classification of these subtypes. Additionally, there is no clear information in the literature about the incidence rate of each subgroup. The most common subgroup is vasomotor rhinitis (VMR) also referred as non-allergic non-infectious perennial rhinitis (NANIPER). Vasomotor rhinitis occurs when the vessels contract or dilate, causing dysfunction of the nerves and muscles [7]. Since its mechanism of occurrence is not clearly understood, some authors call it idiopathic rhinitis (IR). VMR accounts for approximately 71% of all NAR cases, with a worldwide prevalence of approximately 320 million patients [9]. Irritant rhinitis, the most common type of vasomotor rhinitis, is usually associated with smoking. Other types of vasomotor rhinitis with neurogenic etiology are rhinitis associated with environmental humidity and temperature, and gustatory rhinitis and senile rhinitis. Drug-related rhinitis, which is the second most common NAR subtype, is often seen as aspirin and NSAID-related. Additionally, antihypertensives, oral contraceptives and vasodilators are also involved in the etiology of drug-related rhinitis. Rhinitis medicamentosa is also in this group. NARES, neutrophilic rihinitis, occupational rhinitis, hormone-related rhinitis (pregnancy, menstruation, hypothyroidism), rhinitis due to autoimmune diseases constitute other subtypes [2,10].

Occupational rhinitis is characterized predominantly by symptoms of nasal congestion and blockage, sneezing and nasal discharge. It may be related as immunologic (IgE mediated) or non-immunologic mechanisms. In occupational rhinitis, small molecular weight compounds such as aldehydes, isocyanates, plane fuel and jet exhaust, solvents, or cold dry air are common triggers [11,12]. After exposure to these, an immunological response develops in addition to the neurological mechanism, through pro-inflammatory mediators. One study revealed that these patients had significantly increased neutrophil infiltration, myeolperoxidase (MPO), IL-8, nitric oxide (NO) and albumin levels compared to healthy subjects [13].

The most obvious manifestation of hormonal rhinitis occurs during pregnancy. It has been reported that rhinitis symptoms also occur in puberty. In a large multicenter study reporting the rate of hormonal rhinitis during pregnancy as 22%, it was shown that this rate increased to 69% in pregnant women who smoke [14]. In addition, it has been reported in the literature that rhinitis symptoms occur during menstruation. However, no significant relationship has been observed between rhinitis and hormonal diseases such as hypothyroidism and acromegaly [15].

It has been shown that the number of histamine (H1) receptors in the nasal mucosa increases with beta estradiol and progesterone stimulation, and also induces eosinophil infiltration and degranulation. Testosterone has been shown to reverse these effects [16,17].

Drug-related NAR often develops against aspirin or NSAIDs. Their effects can either be isolated rhinitis or manifest as nasal polyps, rhinosinusitis and asthma [11]. However, although it is less common, NAR due to ACE inhibitors, methyldopa and oral contraceptives causes more nasal congestion [11].

NARES is diagnosed with more than 20% eosinophilia in the nasal smear in a patient with symptoms of perennial sneezing attacks, excessive rhinorrhea, nasal itching and partial nasal congestion and loss of smell. In addition, a negative skin prick test and/or absence of increased IgE is also required for diagnosis. Among total NAR cases, NARES has been reported in 13-33% [18]. Generally, nasal polyps and asthma develop in NARES patients [18].

The basic etiological mechanism of NAR is that the nasal mucosa becomes hyperreactive and can be triggered by many types of stimulation. There are studies in the literature revealing autonomic dysregulation that plays a role in the pathogenesis of NAR [1,10]. In understanding the pathogenesis, understanding nasal autonomic innervation becomes important.

Nasal Innervation of the Autonomic System

The surface of the nasal cavity is primarily covered by respiratory epithelium. The lamina propria of this epithelium contains seromucinous acinar glands, blood vessels and nerves [7]. The nerves located here are sympathetic and parasympathetic nerve fibers that play role in nasal autonomic innervation and sensory fibers of nasal mucosa. These nerves coordinate the epithelial, vascular and glandular functioning of the nasal mucosa [19].

Parasympathetic fibers control the activity of the glands located in the nasal mucosa. Presynaptic parasympathetic

fibers are carried by the Vidian nerve. Vidian nerve consists of parasympathetic (greater superficial petrosal nerve) and sympathetic (deep petrosal nerve) fibers. These parasympathetic fibers synapse in the sphenopalatine ganglion. Postsynaptic fibers reach the nasal mucosa [15].

Sympathetic postsynaptic fibers reach the nasal mucosa from the sphenopalatine ganglion. Nasal sympathetic fibers manage the tone of the vessels in the nasal mucosa and the congestion of the turbinates.

Other nerve fibers located in the nasal mucosa are Aδ and C fibers, these are, sensory fibers. These are carried by the ophthalmic and maxillary branches of the trigeminal nerve. These sensory fibers pass through the sphenopalatine ganglion without synapsing and receive the sensations of touch, pain and temperature of the nasal mucosa [15]. Sympathetic activity works through neuropeptide Y and norepinephrine and results in vasoconstriction, increased resistance and decongestion in the nasal mucosa.

C fibers are stimulate by inhaled irritants - such as cigarettes - or stimuli such as environmental humidity and temperature changes. Receptors that detect stimulation of C fibers by these stimuli and play a key role in the pathogenesis of NAR have been identified. There are receptors called TRPA1 -ancrine- and TRPV1 -vanilloid- at the ends of C fibers [20]. TPRV1, one of these receptors, is important in explaining the pathogenesis of NAR. Detailed information about this receptor is provided in the rest of the article.

The C fibers can be peptidergic or non-peptidergic [4,21]. After stimulation of the peptidergic C fibers, activator mediators are released from the nerve endings. Parasympathetic activator mediators such as substance P, acetylcholine and neurokinin 1 activate muscarinic receptors. The main result in these is an increase in glandular secretions, which is the main pathological event in NAR. In addition, it causes vasodilation and extavasation. In this way, rhinitis symptoms such as nasal congestion, rhinorrhea, and postnasal drainage develop [1]. Nasal congestion and rhinorrhea primarily develop due to obstruction of submucosal vascular anastomoses and caverns and increased secretion from goblet cells in serous and mucous glands. Nasal provocation tests performed with capsaicin have shown that there is an increase in glandular secretion, as well as leukocyte infiltration and albumin leakage, depending on the capsaicin dose [22]. As a result of increased parasympathetic stimulation, nasal nonspecific hyperresponsiveness occurs [23]. Nasal hyper-responsiveness is a state of increased nasal sensory and reflexogenic responses, and this response occurs to stimuli such as changes in air temperature and humidity, chemicals used in the home, air pollution or strong odors. A response occurs characterized by rhinorrhea, nasal congestion, sneezing and itching [24,25]. Nasal hyper-responsiveness is also a cardinal feature of NAR, after all, NAR is a disorder thought to result from excessive reactivity of nasal sensory nerves or overinterpretation of signals normally transmitted by CNS response centers [10].

As a result, the balance between parasympathetic and sympathetic responses constitutes the nasal mucosal autonomic system. The shift of balance in the parasympathetic direction is associated with NAR.

The TRPV1 Receptor

TRPV1 receptor is an ion channel located in the membrane of sensor C fibers located in the nasal mucosa. Also known as OTRPC1. It is the most studied member of the transient receptor potential (TRP) superfamily [26]. TRPV1 is known to be activated by capsaicin. However, there are other activators as well. It is activated at high temperatures (>43°C), low extracellular pH, and voltage stimulation, and it opens as an ion channel. [26-28]. Additionally, factors that activate TRPV1 include osmotic stress, or endogenous inflammatory mediators such as histamine, prostaglandins, and lipoxygenase [29,30]. Apart from these, some membrane-derived lipids regulate the function of some ion channels, including TRPV1. It has been shown that TRP channel activity is controlled by the amount of SP and CGRP in the cell [31]. This regulation occurs through a feedback mechanism. Some of these are oleoylethanolamide (OEA), anandamide and some lipoxygenase products [26].

Van Gerven, et al. showed that TRPV1 receptor was found in higher amounts in the nasal mucosa of NAR patients, Substance P was more abundant in their nasal secretions, and the V subfamily of the TRP receptor was more dominant [20].

TRPV1 expression was found to be increased in chronic inflammation. Development of nasal hyperreactivity to environmental triggers has been associated with TRPV1 hyperactivity [32].TRPV1 mediates excitability in airway sensory neurons also. TRPV1 has been shown to contribute to the development of lower and upper airway hyperresponsiveness, bronchoconstriction, and cough [33,34].

As a result of repetitive stimulation of the TRPV1 receptor, degeneration and desensitization occur in C fibers. This is known to lead to its use for various pain treatments such as post-herpetic neuralgia, diabetic peripheral neuropathy, and arthritis-related pain [35].

TRPV1 is specifically activated by capsaicin. Capsaicin is a compound responsible for the “hot” taste of chili peppers.

Additionally, desensitizing of TRPV1 has been shown to have therapeutic value [26]. With the effect of capsaicin, Phosphatidylinositol 4, 5-bisphosphate (PIP2) and its sub-products in the membrane are hydrolyzed and thus TRPV1 becomes N-glycosylated, that is, the stimulation begins [36]. TRPV1 consists of 6 transmembrane protein subfragments. There is a hydrophobic transition zone between the 5^{th} and 6^{th} transmembrane domains in the structure of TRPV1. The outer pore region is the critical region for TRPV channels. This glycosylation causes pore dilatation. Two events occur with por dilation; First, a toxic amount of Ca^{+2} enters the cell, and then conformational changes develop in the outer pore as a cellular protection mechanism. As a result of these changes, the channel begins to become desensitized. Blockage in stimulation develops with desensitization of the TRPV1 ion channel located at the tip of sensor C fibers. In this way, nasal hyperresponsiveness is reduced [37]. Interestingly, glycosylation end products have been found to be elevated in patients with AR, but not NAR [38].

Diagnosis of Non Allergic Rhinitis

There is no standard method yet established for the diagnosis of NAR. The diagnosis of NAR is a diagnosis of exclusion. There is no specific test for this yet. In one study, 98% of patients who were diagnosed as over the age of 45, had no familial history of allergy, had no connection to cats, dogs, furry animals or seasons, and experienced increased arousal in the face of strong olfactory stimuli were diagnosed with NAR, and had negative skin tests performed by allergists. Afterwards, it was determined that the results were compatible with NAR [1]. In addition, the symptoms are frequently triggered by irritants such as smoking, perfume, odor, temperature and humidity changes, but it is not characteristic of all NAR patients to develop a response to all of these triggers [7]. A frequently used method in clinical studies is to induce with CDA (cold dry air) [39]. Previously, capsaicin, menthol, mustard oil, carbon dioxide, ozone, sanshool, toluene, chlorine, air puffs, and thermal stimulation have all been used to investigate nasal neuronal sensitivity [32].

In 1991, Lacroix et al were one of the first studies to use laser Doppler flow measurement to objectively demonstrate improved vascular response to repeated intranasal capsaicin challenge in patients identified with a history of NAR [40]. However, this was not found to be suitable for clinical practice.

One of the methods that has recently been published and is becoming increasingly common in the diagnosis of NAR is optical rhinometry (ORM). Optical rhinometry is based on the Beer-Lambert law, which states that the absorption of light is directly proportional to the concentration and thickness of the sample through which the light penetrates. Working similarly to a pulse oximeter, an ORM device has an infrared radiation detector (mounted on a glasses-like frame) that records any changes in blood flow within the walls of the nasal cavity (intravascular). Its capabilities to measure infrared light pulses with an average wavelength of 600-800 nm allow real-time assessment of changes in intravascular blood flow during the nasal activation provocation test. For this purpose, blood flow measurements are taken from two points at the head of the inferior turbinate and the nasal isthmus [32].

Significant changes were observed in ORM with symptoms of nasal congestion and nasal itching during the nasal provocation test. It was also found to correlate with ORM, anterior rhinomanometry and acoustic rhinometry [7]. The combined use of both ORM and nasal provocation testing has been recognized as a powerful method for diagnosing NAR, but has not yet become widespread [32,41].

In 2012, Lambert et al included 6 NAR and 6 control patients in their study, performed NPT with varying concentrations of intranasal capsaicin (0.005 mM, 0.05 mM, and 0.5 mM) and measured blood flow with ORM. They observed a dose-related increase in optical density in ORM in all NAR patients. In other words, an increase in nasal blood flow reflex was observed, which indicates nasal obstruction. No change was observed in control patients [32].

Capsaicine and Non Allergic Rhinitis Treatment

Many methods have been used in the treatment of NAR, such as oral or local nasal antihistamines, intranasal systemic steroids, and anticholinergics (ipratropium bromide). Other options are capsaicin, intranasal injection of botulinum toxin type A, intranasal saline rinse, local and systemic sympathomimetics and cromolyn sodium. Some treatments may be effective in some types of NAR. For example, ipratropium bromide is often used in elderly patients because rhinorrhea is a major symptom [10]. Intranasal antihistamines are more effective in patients where sneezing and itching are the main symptoms, such as occupational rhinitis [2].

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a naturally occurring alkaloid derived from plants of the Capsicum genus, better known as chili pepper. The molecular formula of capsaicin is C18H27NO3. It is a highly volatile, sharp, hydrophobic, colorless and odorless white crystalline powder [42]. Capsaicin is a TRPV1 ion channel agonist, and reduces excitation of C fibers without affecting Aδ fibers of the trigeminal nerve [7].

The first literature information about the use of capsaicin on the human body dates back to 1878. Hogyes reported a

burning sensation and hyperemia when applied topically to human skin [43]. Subsequent animal studies have reported a decrease in blood pressure, an increase in gastric and salivary gland secretions, and an increase in intestinal activity as a result of intravenous administration of capsaicin [42].

Today, among the properties of capsaicin revealed by many studies conducted on humans in the literature; pain reduction, weight loss, anti-cancer effects, cardiovascular effects (TRPV1 ion channels cause stimulatory pain in the face of myocardial hypoxia. In addition, capsaicin causes vasodilation in some vessels and vasoconstriction in others. It also inhibits platelet aggregation.), gastrointestinal effects (it induces gastrin release). Effects such as, increases the absorption surface area), induction of detrusor muscle contraction by reducing the bladder volume and formation of neurogenic bladder condition, dermatological effects (it is found to be effective in the treatment of psoriasis and pruritic dermatitis) have been determined and taken place in the literature [42].

Capsaicin has been reported to be beneficial in NAR symptom control when administered intranasally [44,45]. There are studies in the literature that chronic intranasal use of capsaicin is effective in symptom control, especially in VMR [1,44,46]. Blom, et al. conducted the first placebo-controlled study on its effectiveness in NAR in 1997 and demonstrated the therapeutic effectiveness of capsaicin [47]. This effect was also noted in a cochrane review [6].

Capsaicin administered intranasally causes activation of TRPV1 receptors located in the nerve ending region of C fibers. As a result, calcium ion (Ca+2) fills the intracellular space and neuronal stimulation is provided. This causes the secretion of neuropeptides in the opposite direction of the message, that is, with an antidromic release. These released neuropeptides create a local inflammatory response. As a result, burning, rhinorrhea, congestion and lacrimation are induced in the nasal mucosa. The mechanism that produces the therapeutic effect is the degeneration and nerve defunctionization caused by massive Ca^{+2} influx into the nerve endings. The need to re-administer capsaicin, that is, the recurrence of symptoms, occurs after several months in many NAR patients. Because of this effect on the neuron, a long refractory period is required for re-excitability. This has led to the wide usage area of capsaicin. The reason for this recurrence is still not clearly known.

However, the level of evidence is stated as low-medium. In this review, the authors agreed that capsaicin is an option that can be used under the guidance of an expert when other options do not work. In this Cochrane review, 5 studies involving 302 patients with moderate-to-severe NAR findings were examined. Of these, 2 studies compared capsaicin with placebo [44,47,48]. A study in the literature compared two different treatment regimens of capsaicin; In one patient group, 5 doses of capsaicin were administered in 1 day, while in the other patient group, 2 or 3 days of treatment was administered for 2 weeks [45]. In another study, in addition to comparison with placebo, 3 different doses of capsaicin were compared with each other and 0.5 mM capsaicin has been shown to cause significant changes in NAR patients [44]. Finally, Havas, et al. compared capsaicin with budesonide and reported that topical capsaicin was significantly more effective than budesonide in symptom control of patients diagnosed with NANIPER [49]. Since there is currently no commercial production of capsaicin in appropriate concentrations, it can be carefully prepared and used by hospital pharmacists [4].

Bernstein et al. showed that low-dose intranasal capsaicin administration for 2 weeks caused a significant reduction in total nasal symptom scores and other symptoms such as headache, sinus pressure and pain, compared to placebo [50].

In a study by Van Gerven L, et al. [20], it was revealed that there was a significant decrease in TRPV1 expression and the amount of SP in NAR patients after repeated applications of capsaicin. This study also showed that 40% of NAR patients could respond after repeated capsaicin administration [20]. The desensitizing effect of capsaicin on TRPV1 channels in trigeminal afferent C fibers may explain its therapeutic benefit in NAR.

In a study comparing capsaicin treatment with placebo in NAR patients, a significant improvement in VAS scores in terms of nasal congestion and sneezing was reported in the capsaicin group, at rates of 64% and 78% at the 4th and 12th week controls, respectively. No significant difference was observed in the control group. This study also revealed that capsaicin treatment did not cause changes such as atrophy/hypertrophy in the glandular structures and did not cause any changes in the integrity of the epithelial layer. No signs of apoptosis were observed after 5 hours or after 12 weeks following capsaicin treatment [20].

Surgical denervation of sensory and autonomic fibers is as effective as intranasal capsaicin in eliminating glandular secretion and mucosal permeability in NAR patients [51]. It has been reported in the literature that the benefit of capsaicin in NAR patients is not in AR patients, and no significant decrease in nasal hyperreactivity or significant improvement in rhinorrhea was observed in patients with AR after intranasal capsaicin application [52].

There are other medications other than capsaicin that have been shown to be effective in NAR patients.

Histamine can activate TRPV1 in sensor C fibers via intracellular phospholipase A2 and lipoxygenase pathways [53]. Therefore, azelastine may be effective in NAR patients by partially desensitizing TRPV1 [7,54]. It has also been shown in another study that locally applied azelastine is effective in symptom control in VMR [55]. Azelastine has received FDA approval for use in NAR.

Fluticasone propionate, one of the nasal corticosteroids, has been shown to be effective in NAR and has received FDA approval [1,8].

Ipratropium bromide, an anticholinergic, has been found to be highly effective in controlling glandular secretion in idiopathic rhinitis, but is ineffective in other symptoms such as nasal obstruction and sneezing [56,57].

Intranasal saline is also effective in reducing symptoms resulting from glandular activation such as rhinorrhea and postnasal drip in NAR patients [58]. Intranasal carbon dioxide has been shown to reduce symptoms in AR patients by regulating TRP channel activity, but this has not yet been studied for NAR [59]. In addition, TRPM8 antagonists, which target TRPM8 located adjacent to TRPV1, have begun to be considered for therapeutic trials in NAR, along with agents such as capsaicin that desensitize TRPV1 ion channels [60].

Separate intranasal and oral applications of SB-705498, a selective TRPV1 receptor antagonist, were observed to block nasal secretion in the rhinitis model. Intranasal SB-705498 has a good safety and preclinical toxicology profile to initiate clinical studies. However, in this study, a 10-fold smaller dose of intranasal SB-705498 was required to achieve the same effect as oral [61]. As a result, TRPV1 antagonists appear as an alternative group of drugs with a safe effect profile that can be used in resistant NAR patients [28].

Intranasal capsaicin administration gives the best results in NAR patients with a high dose as 0.1 mM [6]. Intranasal capsaicin has not become widespread in clinical practice due to its side effects such as pain and burning, requiring local anesthesia beforehand, being time consuming (5 consecutive applications are performed at 1 hour intervals), and its mechanism of action not fully explained [45].

In our literature research, more detailed information about the studies conducted with intranasal capsaicin is written in Table 1.

Author and the publising year of the study	Pathology under investigation	Number of patients and the groups	Capsaicine dosage and the method of using	Follow period	Side effects mentioned	Result
Zebda D, et al. [62] A double blinded RCT	Non allergic rhinitis	Total of 22 patients. (intranasal capsaicin, n=11) and (placebo, n=11)	The drug prepared as 0.1 mMol/L. 2 puffs were applied to each nostril in 5 doses repeated at 1 hour intervals for 1 day. (Each puff 0.4 mL)	Total 12 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported.	At the 4th week, VAS and TSS were decreased, but not statistically significant (p=0.07) At the 12th week, VAS and TSS were decreased statistically significant (p=0.03)
Van Gerven L, et al. [63] A double blinded RCT	Idiopathic rhinitis	Total 68 patients, Group 1:16, Group2:16, Group3: 18 Group3:18	Group 1: 0.1mMol/L (administered in hospital), Group 2: 0.01 mMol/L and Group 3: 0.001 mMol/L doses administered at home, Group 4: Placebo	Total 24 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported.	At weeks 4 and 12, VAS and TRE scores and the amount of Substance P in nasal lavage were significantly lower in Group 1 and Group 2. No significant change was observed in groups 3 and 4.

Van Gerven L, et al. [64] A double blinded RCT	Idiopathic rhinitis	Total 45 participant, 33 of them patients and 12 of them are healthy subjects.	The drug prepared as 0.1 mMol/L. 2 puffs were applied to each nostril in 5 doses repeated at 1 hour intervals for 1 day. (Each puff 0.4 mL)	Total 26 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported	At the end of 26 weeks, the statistically significant decreasing in VAS and TSS scores has showed in capsaicine group.
Van Gerven L, et al. [20] Clinical case series	Idiopathic rhinitis	Total 26 participants, 14 patients and 12 healthy subjects.	The drug prepared as 0.1 mMol/L. 2 puffs were applied to each nostril in 5 doses repeated at 1 hour intervals for 1 day. (Each puff 0.4 mL)	Total 12 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported.	VAS, nasal obstuction and sneezing were signifcantly reduced at 4th week controlVAS, Nasal obstruction, sneezing and rhinorrea were reduced significantly at 12th week control.
Bernstein JA, et al. [50] A double blinded RCT	Non allergic rhinitis	Total 42 participants, Group1: intranasal capsaicine, Group2: placebo	ICX72 nasal spray (Sinus Buster) used twice daily in Group 1.	2 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported	The ISS and TNSS results were significantly reduced after 2 weeks treatment with ICX72 nasal spray.
Ciabatti PG, et al. [44] RCT	Idiopathic rhinitis	Total 208 patients	The drug prepared as 0.1 mMol/L. Group 1:1 µg/ puff, Group 2: 2 µg/puff, Group 3: 4 µg/puff, Group 4: placebo.3 times a day, 30 minutes apart, for 3 consecutive days.	4 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported	Evaluated by daily record chart (DRC). Significant improvement in symptoms in group 3, no significant difference in the others.
Van Rijswick JB, et al. [45] A double blinded RCT	Idiopathic rhinitis	Total 30 patients, Group 1: 5 doses in 1 day, Group 2: 5 doses in 2 weeks	2 puffs were applied to each nostril in 5 doses repeated at 1 hour intervals for 1 day. in Group1. A total of 5 doses every 2-3 days for 2 weeks in Group2	2 weeks	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported	VAS and TSS were found to be significantly decreased in both groups. In addition, insensitivity to triggering by cold dry air has been detected for up to 9 months

Havas, et al. Non randomized CT [49]	Non-infectious perennial rhinitis	Total 40 patients, group 1: 20, group2: 20 patients	The drug prepared as 0.1 mMol/L. Group 1 (20): intranasal budesonide. Group2 (20): intranasal low-dose capsaicine	unknown	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported	The topical capsaicin was significantly more effective than budesonide in controlling symptoms
Blom HM, et al. [48] A double blinded RCT	Non-infectious perennial rhinitis NANIPER	Total 25 patients, 14 of them received capsaicine intranasally and 11 of them received placebo	A total of 7 doses over 2 weeks (total of 0.3 mg intranasal capsaicin per administration)	9 months	By placing lidocaine cotton on the nasal mucosa before application, the discomfort effect on the nasal mucosa was prevented. There were no other side effects reported	No significant changes in cellular components and neuronal structure were observed with nasal biopsies. There was no significant change in the parameters measured in blood and urine. (CD1,CD3CD25,CD68, BMK13, tryptase, chymase, IgE)
Wolf G, et al. [65] Clinical case series	Hyperreactive rhinopathy	123 patients	Capsaicine nasal spray (repeated topical applications of capsaicin solutions in increasing concentrations) Dose is unknown	unknown	No side effects	Self-reported symptoms improved in half to two thirds of patients; average nasal flow and sensitivity to capsaicin improved.
Filliaci F, et al. [66] Clinical case series	Vasomotor rhinitis	10 patients	Topical application of capsaicine using a soaked buffer	6 months	No side effects	This treatment proved to be efficient in reducing nasal reactivity
Eberle L, et al. [67] Clinical case series	Vasomotor rhinitis	84 patients	Low dose nasal spray, dose is unknown.	4 weeks	No side effects	Symptoms improved in most patients. Self-reported symptoms and observer-rated turbinate hypertrophy resolved in half to two thirds of patients, and average nasal flow improved

Riechelmann H, et al. [68] Clinical case series	Non allergic rhinitis	27 patients	Low dose nasal spray, dose is unknown.	6 months	Exanthema of both forearms (2 cases), epistaxis (1 case) and increased dryness of the nasal mucosa; nasal obstruction, hypersecretion, nasal itching, sneezing, mucosal dryness and headache (22 cases)	Intranasal capsaicin has been found to be beneficial in patients with prominent sneezing and rhinorrhea complaints and mild obstruction complaints.
Marabinil S, et al. [69] Clinical case series	Vasomotor rhinitis	20 patients	3 doses per day for 3 consecutive days, 15 micrograms of content per dose.	1 month	No side effects.	Nasal obstruction and rhinorrea scores were markedly reduced after treatment
Lacroix JS, et al. [40] Clinical case series	Non-allergic rhinitis	16 patients	3,3 micromol of dose, intranasally, once weekly for 5 weeks	6 months	No side effects	Both the subjective symptom score and objective measurements of vascular reactivity showed that this drug is benefical for NAR

Table 1: Publications in the literature containing intranasal capsaicin.

Table 1: Detailed information about studies conducted with randomized controlled and/or clinical case examples in the literature is included in the table. (VAS: Visual analogue scale, TSS: Total symptom score, TRE: Treatment response evaluation, ISS: participant symptom score, TNSS: Total nasal symptom score).

As a result, In order to determine the safe dose for intranasal administration, different doses need to be reviewed with in vitro studies. Capsaicin will take its rightful place in the treatment of NAR patients after the number of patients is high enough in in vivo studies and the safe dose range can be determined and preparations can be created for home use.

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