

# Botulinum Toxin for Rhinitis

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## Abstract

**Purpose of Review** Rhinitis is a common clinical entity. Besides nasal obstruction, itching, and sneezing, one of the most important symptoms of rhinitis is nasal hypersecretion produced by nasal glands and exudate from the nasal vascular bed. Allergic rhinitis is an IgE-mediated inflammatory reaction of nasal mucosa after exposure to environmental allergens. Idiopathic rhinitis describes rhinitis symptoms that occur after non-allergic, noninfectious irritants. Specific allergen avoidance, topical nasal decongestants, nasal corticosteroids, immunotherapy, and sinonasal surgery are the main treatment options. Because the current treatment modalities are not enough for reducing rhinorrhea in some patients, novel treatment options are required to solve this problem.

**Recent Findings** Botulinum toxin is an exotoxin generated by *Clostridium botulinum*. It disturbs the signal transmission at the neuromuscular and neuroglandular junction by inhibiting the acetylcholine release from the presynaptic nerve terminal. It has been widely used in neuromuscular, hypersecretory, and autonomic nerve system disorders. There have been a lot of published articles concerning the effect of this toxin on rhinitis symptoms. Based on the results of these reports, intranasal botulinum toxin A administration appears to be a safe and effective treatment method for decreasing rhinitis symptoms in rhinitis patients with a long-lasting effect.

**Summary** Botulinum toxin type A will be a good treatment option for the chronic rhinitis patients who are resistant to other treatment methods.

**Keywords** Rhinitis · Allergic rhinitis · Vasomotor rhinitis · Idiopathic rhinitis · Botulinum toxin A

## Introduction

Rhinitis can be described as the inflammation of the nasal mucous membranes. It is characterized by at least one of the symptoms of nasal discharge, nasal obstruction, itching, and sneezing which occur two or more consecutive days for more than 1 h [1•, 2]. It is a common disease and influences approximately 20 % of the population. Its incidence is increasing and it represents an important health problem. Rhinitis can be categorized into infectious, allergic, occupational, drug-induced, hormonal, idiopathic, and others [1•]. Because rhinitis patients are not a uniform group, there is no globally accepted definition of subclasses. Rhinitis can also be classified as allergic, infectious, and “other” rhinitis groups. Other rhinitis group contains idiopathic rhinitis, NARES, occupational rhinitis and etc. [2, 3, 4•, 5•]. Idiopathic rhinitis is also known as non-allergic, noninfectious perennial rhinitis, intrinsic, or vasomotor rhinitis [3]. In this review, idiopathic rhinitis (IR) was used as a synonym of vasomotor and intrinsic rhinitis. Allergic rhinitis (AR) can be delineated as an inflammatory disorder of the nasal mucosa induced after allergen exposure by an IgE-mediated immune response [1•]. IR accounts approximately 50 % of all types of chronic rhinitis and it is a diagnosis of exclusion. Although the underlying etiopathogenesis is not fully understood, an autonomic nervous system imbalance with an effect of relatively dominant parasympathetic system in the nasal mucosa is supposed. Nasal

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blockage and rhinorrhea are commonly seen, whereas itching and sneezing symptoms are not as common as AR [3].

### Neuroregulation of Nasal Cavity

Nasal patency and secretion is predominantly under the control of the autonomous nervous system. Preganglionic parasympathetic neurons in the fibers of the greater petrosal nerve enter the sphenopalatine ganglion to synapse with the postganglionic neurons. The postganglionic sympathetic nerves become deep petrosal nerves and join the preganglionic parasympathetic nerves of the greater petrosal nerve in the vidian canal. The combined nerve fibers of parasympathetic and sympathetic nervous system form the vidian nerve. Seromucinous secretion is controlled primarily by the parasympathetic nervous system, whereas vascular tone is mainly controlled by the sympathetic nerves [6•]. The nose has abundant capillary networks to provide the metabolic needs of the epithelial cells and promote heat and water exchange. There is a marked capacitance vessel (sinuses) that has the ability to expand and contract the nasal mucosa. These capacitance vessels are under the control of the autonomic nervous system by the effect of various neurotransmitters. The parasympathetic nervous system induces a vasodilatory effect on the nasal mucosa and decreases the nasal patency, whereas the sympathetic nervous system has a vasoconstrictor effect and increases the nasal airway. Acetylcholine (ACh), vasoactive intestinal peptide (VIP), and nitric oxide are the main parasympathetic neurotransmitters, whereas noradrenaline (NA) and neuropeptide Y are the main sympathetic neurotransmitters [7].

The origin of nasal mucus secretion is from three sources: nasal submucosal seromucous glands, goblet cells, and serous cells in the mucosal epithelium. Nasal mucus secretion in the nose is under the control of the parasympathetic nervous system. Acetylcholine is the principal neurotransmitter of the parasympathetic system. Increased parasympathetic activity causes increased nasal mucus secretion and nasal discharge which is the main reason of rhinorrhea symptom of rhinitis patients. Sympathetic nervous system neuromediators include NA and neuropeptide Y. They mostly modulate the secretion initiated by the parasympathetic nervous system rather than the direct effect [7].

Besides autonomic neuronal control of the nasal mucosal vasculature and submucosal glands, some sensory neuropeptides also take part in the pathogenesis of nasal obstruction and rhinorrhea in rhinitis patients. Activation of sensory nerve endings and C-fiber receptors causes release of sensory neuropeptides such as substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP). These mediators have the ability to increase vascular permeability and mucus secretion, cause vasodilatation, and mast cell degranulation which contribute to the rhinorrhea and nasal obstruction [7,

8]. Nociceptive type C fibers of the trigeminal nerve and sensory neuropeptides (SP, NKA, CGRP) are also responsible for the itching and sneezing reflexes in rhinitis patients [9].

All rhinitis patients have nasal hyperactivity with different importance. Treatment of nasal hyperactivity is dependent on the type of the rhinitis and the other complaints of the patients. Allergen avoidance, topical nasal decongestants, nasal corticosteroids, immunotherapy, and sinonasal surgery are the main treatment options. Because these therapeutic interventions are not enough for reducing rhinorrhea, novel treatment options should be developed.

### Botulinum Neurotoxin

Botulinum toxin (BTX) is a neurotoxin produced by *Clostridium botulinum*, a Gram-positive anaerobic bacillus [10]. It affects the signal transmission at the neuromuscular and neuroglandular junction by blocking the acetylcholine release from the presynaptic nerve terminal [10]. There have been eight distinct BTX serotypes named as A to H, whereas the recent H form is questionable [11]. Most authors accepted seven immunologic subtypes (A–G) [12]. The rationale of its use in medicine is derived from its neurotransmitter release inhibition effect at the neuromuscular junction. BTX type A (BTX-A) has the most powerful anticholinergic effect at the neuromuscular junction [3]. It is a metalloprotease that binds specifically to neurons, internalized at the neuromuscular junction, binds specifically to synaptosomal-associated protein with a molecular weight of 25 kd. (SNAP-25) protein, and prevents exocytosis of the neurotransmitters after cleaving this protein [3, 12, 13]. It blocks the release of presynaptic acetylcholine from cholinergic nerve endings. Cholinergic parasympathetic and postganglionic sympathetic nerve synapses are reluctant to BTX treatment [13]. Its effects are temporary and dose-dependent [14]. Recently, the usage of BTX-A have been increased rapidly in a wide range of diseases because of the understanding of the physiology of BTX as well as its improved efficacy and safety. BTX inactivates the functions of the muscles or glands. Except for cosmetic applications, conditions including involuntary muscle spasms such as strabismus, spasmodic dysphonia, cervical dystonia, spasmodic torticollis, bruxism, blepharospasm, hemifacial spasm, palatal myoclonus, and temporomandibular joint disorders are good indications for BTX treatment [14]. BTX can also be used for hypersecretory and autonomic nerve system disorders such as sialorrhea, hyperhidrosis, hyperlacrimation (epiphora), chronic sialoadenitis, gustatory sweating, and Frey's syndrome [10, 15, 16].

The effect of BTX-A on the mucosal lining of the nose has been suggested in four possible mechanisms:

1. Suppression of release of acetylcholine from the cholinergic nerve endings in the nasal mucosa

2. Inhibition of release of acetylcholine from preganglionic cholinergic nerve endings in the sphenopalatine ganglion
3. Initiation of apoptosis of the nasal submucosal glands
4. Decreasing the release of neuropeptides such as VIP and SP from the trigeminal and parasympathetic nerve endings [17, 18]

## Botulinum Toxin for Allergic Rhinitis

AR is an IgE-mediated inflammatory reaction of nasal mucosa after exposure to environmental allergens. The major mediator of nasal inflammation in AR is histamine that causes symptoms with increasing of vascular permeability, leakage from blood vessels, mucus secretion, and stimulating the sensory nerve terminals. The other mediators such as neurokinin A, SP, CGRP, VIP, and neurotrophins (nerve growth factor, brain-derived neurotrophic factor, neurotrophin 3) also take part in cascade reactions [8]. AR is the most common type of chronic rhinitis, but 30–50 % of cases with chronic rhinitis have non-allergic irritants and 44–87 % of cases with rhinitis may have mixed rhinitis with a combination of allergic and non-allergic rhinitis [19].

## Experimental Studies

Some studies have been designed to assess the effect of intranasal BTX application on the nasal symptoms and mucosal histopathological changes in the experimental AR models. Application of the toxin had been done by turbinate injection or topical sponge soaked with BTX, nasal drip infusion, or gel form. Recently, Aoishi and colleagues [20] demonstrated the effect of single-dose nasal drip infusion of BTX-A on ovalbumin-sensitized mice. They found that 10- $\mu$ L single-dose BTX-A application decreased number of sneezes, nose scratches, mucosal edema, eosinophil infiltration, and nasal secretion for 3 weeks.

Rohrbach and colleagues showed that intranasal application of sponge embedded with BTX-A initiated apoptosis of nasal submucosal glands in the guinea pigs [21•]. This apoptotic effect was seen after 10 days of BTX usage but not 3 months. They concluded that the shorter duration of BTX-A effect on the nasal mucosa compared to effects on the neurologic muscle diseases, gustatory sweating, and hyperlacrimation may be explained by the existence of abundant vascular network in the nasal cavity which causes absorption and clearance of BTX more rapidly [21•]. Wen and colleagues [17] found that cotton strips soaked with 20 U of BTX-A applied to nasal cavity of ovalbumin-sensitized rats decreased inflammatory reactions, SP, VIP expression in the nasal mucosa, and submucosal gland atrophy. Gunes and colleagues [22] also found that inferior turbinate injection of 10 U

of BTX-A decreased nasal secretion and histologic findings such as vascular proliferation, congestion, and connective tissue proliferation in ovalbumin-sensitized rabbits. Zhu and colleagues [23] suggested that the nasal topical gel form of BTX-A can be safely used in decreasing rhinitis symptoms in the rat AR model. They also showed that the topical gel form also has inhibitory effects on the inflammatory signs of nasal mucosa in rats.

## Clinical Studies

Some clinical studies were also performed to evaluate the effect of BTX on AR symptoms, especially rhinorrhea (Table 1). There is no universally accepted dose for intranasal BTX usage; 40–200 U of BTX-A doses have been applied for the relief of nasal symptoms in different studies. Application types of usage are topical sponge soaked with BTX-A, nasal septal submucoperichondrial, inferior, and middle turbinate injection. Unal and colleagues [25•] found that turbinate injection of 40 or 60 U of BTX-A decreased AR symptom scores for rhinorrhea, nasal obstruction, and sneezing for 8 weeks. Itching scores were lower than those of the control group only for 2 weeks. They reported no complication and side effects. Total symptom scores were similar in the 40 and 60 U usage. Yang and colleagues [27] compared the turbinate injection of in total 50 U BTX-A with 40-mg triamcinolone in AR patients. Each method was effective than the control group, but the BTX-A group had a long-lasting effect up to 20 weeks for all symptoms of rhinitis. They also reported no side effects like nasal dryness, epistaxis, or muscular palsy.

Abtahi and colleagues [31] compared the intraturbinate and septal BTX-A injections in AR patients. They found that 80 U of application of BTX-A of the nasal cavity in each group decreased rhinorrhea, nasal obstruction, and sneezing scores but had no effect on itching or eye symptoms. The posttreatment symptom scores were the same in both groups. Complication rates were 16 % in the turbinate group (three patients had epistaxis, one patient had nasal mucosa dryness) and 4 % (one patient had epistaxis) in the septal group. They concluded that nasal BTX-A administration is effective in AR symptoms in the two groups, but septal injection is easier and safer compared to turbinate injection. Mozafarinia and colleagues [34] also mentioned that nasal septal BTX injection is safer than turbinate injection. They reported that 80 U of nasal septal submucoperichondrial injection of BTX-A had no side effects and a longer duration of action compared to turbinate injection. They argued that since the turbinates have much more blood supply compared to nasal septum, lesser clearance of the BTX-A by bloodstream after septal injection had caused longer duration of action. Hashemi and colleagues [32] compared the effect of once daily 10 mg cetirizine with 75 BTX-A U injection to each inferior turbinate in AR patients. They found that both methods were effective for all

**Table 1** Clinical studies investigating the effect of BTX-A on rhinitis symptoms

| Author                 | Publishing date | Rhinitis type and no. of study group | Type of application                                                      | BTX-A type and dosage                    | Side effect                                                                                    | Result                                                                                                                                           |
|------------------------|-----------------|--------------------------------------|--------------------------------------------------------------------------|------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Kim et al. [18]        | 1998            | IR, 60                               | Inferior and middle turbinate injection                                  | Botox <sup>®</sup> , 8 U                 | None                                                                                           | BTX-A decreased rhinorrhea for 4 weeks, but did not affect nasal obstruction or sneezing.                                                        |
| Rohrbach et al. [24]   | 2001            | IR, one case report                  | BTA soaked sponge application in a case report                           | Botox <sup>®</sup> , 40 U                | Occasional nasal dryness                                                                       | BTX-A decreased both rhinorrhea and nasal obstruction for 4 weeks.                                                                               |
| Unal et al. [25•]      | 2003            | AR, 34                               | Inferior and middle turbinate injection                                  | Botox <sup>®</sup> , 40–60 U             | None                                                                                           | Both BTX-A doses were effective in decreasing symptoms for 8 weeks except itching.                                                               |
| Wang et al. [26]       | 2003            | IR, 32                               | Turbinate injection (patients)<br>Sponge soaked application (guinea pig) | ??????? 10 U(topical)<br>20 U(injection) | Nasal dryness                                                                                  | BTX-A induced degeneration of glands in animals; it is effective on rhinorrhea of patients with IR.                                              |
| Ozcan C [3]            | 2006            | IR, 30                               | Inferior and middle turbinate injection                                  | Botox <sup>®</sup> , 10 and 20 U         | None                                                                                           | Both BTX-A doses are effective in decreasing all nasal symptoms except itching. 20 U of BTX-A is also effective on itching after the first week. |
| Yang et al. [27]       | 2008            | AR, 39                               | Inferior and middle turbinate injection                                  | Botox <sup>®</sup> , 50 U                | None                                                                                           | BTX-A is more effective than steroid injection for nasal symptoms. The effect prolongs to 20 weeks.                                              |
| Sapci et al. [28]      | 2008            | IR, 38                               | Turbinate injection                                                      | 20 U                                     | None                                                                                           | BTX-A injection is as effective as ipratropium bromide in the controlling of rhinorrhea for 8 weeks.                                             |
| Rohrbach et al. [4•]   | 2009            | IR, 17                               | BTA soaked sponge application for 30 minutes                             | Botox <sup>®</sup> , 80 U                | None                                                                                           | BTX-A decreased rhinorrhea for 12 weeks.                                                                                                         |
| Nowak et al. [29]      | 2011            | IR, 17                               | Inferior and middle turbinate injection, Merocel soaked with BTX         | Botox <sup>®</sup> , 10, 20, and 40 U    | –                                                                                              | Both BTX-A injection and topical usage are effective in decreasing rhinorrhea symptom for 8–12 weeks.                                            |
| Braun et al. [30•]     | 2012            | IR, 5                                | Septal submucoperichondrial injection                                    | Dysport <sup>®</sup> , 80 U              | None                                                                                           | Septal BTX-A injection is also effective in decreasing nasal symptoms of IR patients.                                                            |
| Abtahi et al. [31]     | 2013            | AR, 50                               | Inferior turbinate and nasal septal injection                            | Dysport <sup>®</sup> , 80 U              | 12 % epistaxis and 4 % nasal dryness in the turbinate group, 4 % epistaxis in the septal group | Both intratubinal and septal BTX-A injection decreased rhinorrhea, sneezing, and nasal congestion.                                               |
| Hashemi et al. [32]    | 2013            | AR, 50                               | Inferior turbinate injection                                             | Dysport <sup>®</sup> , 150 U             | 4 % nasal dryness, 4 % epistaxis                                                               | BTX-A is effective on the nasal symptoms. BTX-A is also effective on the eye symptoms when compared with cetirizine.                             |
| Shemshadi et al. [33]  | 2013            | AR, 44                               | Topical application with nasal sponge                                    | Dysport <sup>®</sup> , 200 U             | None                                                                                           | BTX-A-soaked sponge is effective for controlling AR symptoms.                                                                                    |
| Mozafarina et al. [34] | 2015            | AR and IR, 40                        | Nasal septal                                                             | Dysport <sup>®</sup> , 80 U              | None                                                                                           | Septal BTX-A injection is a safe and effective method for controlling rhinitis symptoms.                                                         |

AR allergic rhinitis, BTX-A botulinum toxin A, IR idiopathic rhinitis

nasal symptoms. They also reported that BTX-A was more effective for eye symptoms, whereas cetirizine was more effective for nasal itching. The cetirizine group had more side effects like sleepiness and blurred vision. Shemshadi and colleagues [33] used topical BTX-A application with 100 U of embedded 5-cm nasal sponge to both nasal cavities. They found that topical application was also effective against rhinorrhea, sneezing, and itching for 12 weeks. Decrement in rhinorrhea and sneezing scores was more marked when compared to itching.

### Botulinum Toxin for Idiopathic Rhinitis

Idiopathic rhinitis is the term used to define the rhinitis symptoms that occur after non-allergic, noninfectious irritants like humidity, emotional and physical stress, temperature and pressure changes, strong smells, cigarette smoke, and ingestion of some foods. It is a diagnosis of exclusion after the elimination of anatomic, infectious, immunologic, drug-induced, endocrinologic, metabolic, vascular, or atrophic causes [35, 36]. The underlying pathogenesis is not fully understood, but it is suggested to be the result of autonomic nervous system dysfunction with a predominance of the parasympathetic nervous system in the nasal mucosa [35, 36]. Local IgE synthesis without systemic allergy and nociceptive dysfunction are the other possible mechanisms. It is the most common non-allergic rhinitis type (~70 % of all cases), with female predominance. It is clinically characterized by nasal obstruction, increased nasal discharge, and less common sneezing and itching. IR patients with predominant nasal discharge symptoms are called “*nasal runners*,” whereas patients with nasal obstruction as the main symptom are called “*blockers*” [35].

Shaari and colleagues [6•] performed an experimental study for controlling rhinorrhea with topical nasal BTX-A application in dogs. They stimulated the sphenopalatine ganglion by bipolar needle electrically to produce nasal hypersecretion after 6 days of nasal 50 U BTX-A-soaked sterile gauze application in four dogs. They experienced an average of 41 % reduction in rhinorrhea in the BTX-A group.

In 1998, Kim and colleagues [18] firstly demonstrated the effect of BTX-A intranasal injection on 60 patients with IR. They showed that rhinorrhea decreased nearly 25–40 % for 4 weeks after a total of 8 U intratubinal BTX-A administration without side effects. BTX-A usage did not have an effect on the symptoms of nasal obstruction or sneezing.

Rohrbach and colleagues [24] presented an IR patient unresponsive to nasal steroid and local decongestant and antihistaminic treatment. They applied 20 U of BTX-A-embedded sponge on each site of the nasal cavity for 30 min. They reported that rhinorrhea, nasal obstruction, and sneezing symptoms were decreased after BTX-A application with occasional nasal dryness. After this case report, they also

conducted a prospective study showing the effect of BTX-A-embedded sponge administration in 17 patients with IR in 2009 [4•]. They applied 40 U of BTX-A in both nasal cavities (total of 80 U). They concluded that local sponge-soaked application of BTX-A can also be used instead of injection methods to achieve a long-lasting (up to 12 weeks) decrement in nasal hypersecretion.

Ozcan and colleagues [3] demonstrated the effect of intratubinal injection of BTX-A in 30 IR patients. They injected a total of 10 (15 patients) and 20 U (15 patients) of BTX-A into the inferior and middle turbinates on each side of the nasal cavity. They concluded that both intratubinal 10 and 20 U of BTX-A injections decreased rhinorrhea, nasal obstruction, and sneezing scores in IR patients without side effects.

Sapci and colleagues [28] compared the effect of intratubinal BTX-A injection with nasal topical ipratropium bromide application in 38 IR patients for controlling rhinorrhea complaint. They presented that both nasal topical ipratropium bromide spray and intratubinal BTX-A injection are effective and safe methods for nasal discharge symptom in patients with IR.

Recently, Braun and colleagues [30•] presented their results of nasal septal submucoperichondrial BTX-A injection in five patients with IR. They injected 20 U of BTX-A on two sites of nasal septum on each nasal cavity (total of 80 U) doses. They suggested that septal injection is a safe method without side effects for decreasing nasal symptoms of IR for 2 weeks.

The main effect of BTX in rhinitis patients is on rhinorrhea symptom, but some patients with excess nasal discharge do not respond to BTX treatment. This situation may be explained by that acetylcholine has a minor effect on nasal secretion in some patients. Rohrbach and colleagues designated the “*BTX-A sensitive rhinitis*” term for the patients with rhinitis who benefit from BTX to differentiate them from other non-allergic rhinitis patients [4•].

### Conclusion

Intranasal administration of BTX-A through different ways and doses seems to be a safe and effective treatment option for controlling rhinitis symptoms, especially rhinorrhea, in allergic and idiopathic rhinitis patients with a long-lasting action. BTX-A may be a good alternative for the treatment of rhinitis patients who are unresponsive to other treatment methods. Some restrictions such as high cost, painful injections, and needing of specialized experience for administration prevents its wide usage. Larger studies with extended follow-ups are needed to determine the duration of effect and optimal dosage of BTX-A.

## Compliance with Ethical Standards

**Conflict of Interest** Drs. Ozcan and Ismi declare no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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