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THE NEW FACE OF AN OLD TOXIN: BOTULINUM TOXIN IN THE PREVEN-TION OF POST-OPERATIVE HEART RHYTHM DISORDERS

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ABSTRACT

Botulinum toxin, previously used mainly in neurology and aesthetic medicine, is increasingly finding application in new fields, including cardiology. Its ability to selectively and temporarily block cholinergic conduction makes it a promising tool for modulating the activity of the auto-nomic nervous system, which is important in the prevention of postoperative atrial fibrillation (POAF). Atrial fibrillation is one of the most common postoperative complications in cardiac surgery, significantly affecting the course of recovery and patient prognosis. An imbalance be-tween sympathetic and parasympathetic regulation of the heart rhythm plays a significant role in the pathogenesis of this disorder. This paper reviews the current state of knowledge on the ther-apeutic potential of botulinum toxin in the prevention of POAF. The data indicate that the use of botulinum toxin may lead to a reduction in the incidence of postoperative arrhythmias in select-ed patient groups. The need for further research to determine the optimal treatment regimen and identify the patient population most likely to benefit from this type of therapy was also empha-sised.

KEYWORDS

Botulinum Toxin Type A, Post-Operative Atrial Fibrillation (POAF), Supraventricular Arrhythmias, Autonomic Nervous System, Epicardial Adipose Tissue

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Introduction

Botulinum toxin – general characteristics and clinical significance

Botulinum toxin (BoNT) is increasingly used for therapeutic purposes. Although it gained its greatest popularity through applications in aesthetic medicine, its clinical potential extends far beyond the field of cosmetology [1]. The origins of research on the toxin date back to the 19th century. In 1817, the German physician Justinus Kerner was the first to describe its effects based on analyses of botulism poisoning cases. Later, in 1897, Emile Pierre van Ermengem isolated the bacterium Clostridium botulinum as the etiological agent of botulism. The clinical use of BoNT, however, began only in the 1970s, when Alan Scott conducted the first therapeutic trials for the treatment of strabismus [2,3]. Subsequently, the toxin found therapeutic application in a range of other movement disorders and autonomic system dysfunctions. In later years, it received FDA (Food and Drug Administration) approval for the treatment of blepharospasm, cervical dystonia, and facial nerve paralysis [4]. The first therapeutic indications mainly involved the inhibition of cholinergic transmission in the somatic nervous system, particularly at neuromuscular junctions [2].

The aim of this study is to present the current state of knowledge on the use of botulinum toxin in the prevention of POAF in patients undergoing cardiac surgery. It discusses the mechanisms by which botulinum toxin acts in modulating the cardiac autonomic nervous system, reviews available clinical trial data, and evaluates the safety and efficacy of this approach. In addition, potential directions for further research were indicated and an attempt was made to identify clinical characteristics that may predispose patients to derive the greatest benefit from this type of therapy.

Materials and methods

This paper is a review article. The literature review was conducted based on scientific publications from 2005 to 2025, retrieved from the PubMed, Scopus, and ScienceDirect databases. The following combinations of keywords were used for the search: botulinum toxin, atrial fibrillation, cardiology, autonomic nervous system. Original papers, review articles, current guidelines and meta-analyses on the use of botulinum toxin in cardiology were included, with particular emphasis on the prevention of postoperative atrial arrhythmias. The search yielded 100 articles, of which 10 were selected for review.

Mechanism of Action of Botulinum Toxin

Botulinum toxin (BoNT) is a potent neurotoxin produced by the anaerobic bacteria Clostridium botulinum. There are seven serotypes of this toxin (A–G), of which BoNT-A and BoNT-B are of greatest clinical significance [5]. The key mechanism of action of the toxin is to inhibit the release of acetylcholine from presynaptic terminals within the somatic and autonomic nervous systems [6].

After administration, the toxin selectively binds to receptors on the surface of cholinergic nerve terminals. Subsequently, BoNT is internalized through endocytosis. Structurally, botulinum toxin consists of two chains: a heavy chain (H), responsible for recognition and transport of the toxin into the cell, and a light chain (L), which, upon entering the cytoplasm, exerts enzymatic activity [7].

The light chain of BoNT is a zinc-dependent endopeptidase that cleaves proteins of the SNARE complex, a key component of the neurotransmitter release process at the synapse. The SNARE complex (soluble NSF attachment protein receptor) comprises proteins involved in the docking and fusion of synaptic vesicles with the neuronal membrane, enabling the exocytosis of acetylcholine into the synaptic cleft. The principal targets of botulinum toxin include SNAP-25 in the case of BoNT/A and synaptobrevin (VAMP) in the case of BoNT/B. Proteolytic cleavage of these proteins prevents proper vesicle fusion with the presynaptic membrane, ultimately leading to inhibition of neurotransmission [7,8].

Blocking this process leads to a temporary and reversible blockage of cholinergic conduction [9]. In the somatic system, this results in a reduction in skeletal muscle tone, while in the autonomic system, it results in the modulation of the functions of organs innervated by sympathetic and parasympathetic fibres [9]. The effect of the toxin usually appears after a few days, reaches its maximum within 1–2 weeks and lasts for a period of 3 to 6 months, followed by a gradual restoration of neurotransmission [10].

Owing to its ability to selectively and reversibly block nerve transmission, BoNT has found wide application in the treatment of neurological, ophthalmological, dermatological, and autonomic disorders [1].

Adverse Effects

Adverse effects of BoNT depend on the dose, injection site, administration technique, and individual patient susceptibility. An analysis of reports submitted to the FDA, conducted by T.R. Coté (2005), showed that the most frequently reported complications involved the central and peripheral nervous systems. Reported symptoms included muscle weakness, cranial nerve palsies, dizziness, as well as cases of ptosis, diplopia, and paresthesia. Less frequently, gastrointestinal and respiratory symptoms were observed, including dysphagia, dry mouth, pneumonia, and instances of pulmonary embolism. In some cases, the effect of the toxin extended beyond the injection site, leading to generalized symptoms resembling botulism, such as symmetrical skeletal muscle weakness, hypoventilation, and even respiratory failure [11].

As reported by Jankovic et al. (2004) and Naumann et al. (2008), systemic adverse effects are observed mainly after the administration of high doses or in cases of accidental intravascular injection. In clinical studies, the most commonly reported reactions were mild and included headache, flu-like symptoms, and local pain or swelling at the injection site. The vast majority of adverse effects are transient and resolve within a few days to several weeks [12,13].

Botulinum toxin type A is generally well tolerated, and its safety profile has been confirmed in numerous clinical trials and meta-analyses. Nevertheless, in 2009, the U.S. Food and Drug Administration (FDA) introduced a requirement to include warnings about the risk of systemic toxin effects, particularly in children and in patients with neuromuscular disorders [14].

Botulinum Toxin in Cardiology

Because of its capacity to modulate the autonomic nervous system by inhibiting cholinergic signaling, botulinum toxin is gaining growing attention as a therapeutic option in cardiology, especially for the prevention of POAF.

Postoperative Atrial Fibrillation

The autonomic nervous system (ANS) plays a crucial role in the pathophysiology of atrial fibrillation (AF), both in its chronic and postoperative (POAF) forms. A key role is attributed to the ganglionated plexi (GP), located primarily within the epicardial adipose tissue. These structures are most commonly found around the pulmonary vein ostia, the aortic root, and along the atrioventricular groove. The ganglionated plexi modulate atrial electrical activity, and their excessive activation promotes the initiation of arrhythmias [15,16].

The epicardial adipose tissue (EAT), in which the ganglionated plexi (GP) are embedded, also contributes to the pathogenesis of atrial fibrillation (AF). EAT is located between the epicardium and the outer layer of the myocardium, lying directly on the heart surface. The largest accumulation of this tissue is observed in the coronary sulcus, interventricular septum, and at the base of the great vessels [16]. These effects result from the secretion of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), adipokines, and free fatty acids, which modulate electrical conduction and promote fibrosis [17].

The interplay between EAT and ganglionated plexi (GP) further enhances the arrhythmogenic effects of these structures. Inflammatory mediators released from EAT may increase ganglionic excitability and promote the initiation of AF. Thus, both GP and EAT play a crucial role in the pathophysiology of AF and are considered potential therapeutic targets [18].

EAT functions not only as a lipid reservoir but also as an active metabolic and immune tissue. It harbors immune cells, including macrophages and T lymphocytes, whose activation contributes to inflammation and structural changes in the atria. Moreover, EAT promotes fibrogenesis by stimulating fibroblasts and enhancing collagen production, leading to a non-uniform electrical substrate that supports the persistence of AF [18,19].

Stimulation of the ganglionated plexi (GP) leads to shortening of the action potential duration in atrial cardiomyocytes, which facilitates the formation of ectopic foci and promotes the development of AF [20]. Cholinergic stimulation modifies the repolarization process, whereas sympathetic activation enhances calcium release from the sarcoplasmic reticulum, resulting in electrical instability and an increased susceptibility to arrhythmias [21]. The activity of the GP is also influenced by inflammatory cytokines released in response to surgical injury [22].

According to various analyses, POAF occurs in approximately 30–40% of patients undergoing cardiac surgery. It may lead to complications such as hemodynamic instability, heart failure, and stroke. Pharmacological therapy shows limited efficacy and is associated with adverse effects, including bradycardia and bleeding [23].

The thickness and distribution of EAT correlate with the risk of paroxysmal and persistent AF, independently of traditional risk factors such as age and hypertension [24]. EAT stromal cells, activated via muscarinic receptors, enhance local inflammation and metabolic disturbances, thereby increasing the susceptibility of the atria to arrhythmias [25].

Modern imaging techniques are increasingly used for quantitative and qualitative assessment of EAT. These include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and other nuclear medicine methods. In parallel, electroanatomical mapping and targeted ablation of ganglionated plexi (GP) are being developed. These approaches may, in the future, complement therapeutic strategies in selected patients with atrial arrhythmias [26,27].

Temporary neuromodulation using botulinum toxin type A (BoNT/A) represents a potential alternative to pharmacological therapy. Its transient duration of action coincides with the period of highest risk for POAF. Given the multifactorial etiology of this disorder, BoNT may be most effective as part of a combined therapeutic strategy [2,6,7].

POAF may also occur in an asymptomatic form. The so-called silent POAF refers to arrhythmic episodes that remain undetected during routine clinical evaluation, being identified only through continuous telemetry monitoring. Despite the absence of clinical symptoms, such episodes have important prognostic implications, as they increase the risk of thromboembolic complications, including ischemic stroke. Moreover, they may indicate heightened inflammatory activation and contribute to the progression toward persistent forms of atrial fibrillation (AF) [28].

Incidence of POAF by Type of Surgery

After Cardiac Surgery	After Thoracic Surgery	After Other Types of Surgery
Valve surgery: 40–50%	Pneumonectomy: ~30%	0.4%–15%
Aortic surgery: 30%	Overall: ~15%	
Overall: 30%		

Studies

One of the first clinical trials evaluating the efficacy of botulinum toxin in the prevention of POAF was a pilot study conducted by Pokushalov et al. in 2014. In this study, 60 patients with paroxysmal AF undergoing coronary artery bypass grafting (CABG) received intraoperative injections of either botulinum toxin (50 U/ml) or placebo (0.9% NaCl) into the EAT. Within 30 days after surgery, POAF occurred in only 7% of patients in the BoNT group, compared with 30% in the placebo group ($p = 0.024$). Importantly, during 12 months of follow-up, none of the patients treated with BoNT experienced a recurrence of arrhythmia, whereas 27% of patients in the placebo group did [30]. After three years, a significantly lower arrhythmia burden was still observed in the BoNT group, suggesting a long-term therapeutic effect. No increase in adverse events or deterioration in respiratory function was reported, and parameters such as pulmonary performance, inflammatory biomarkers, and rehospitalization rates confirmed the good tolerability of the therapy [31].

The largest study to date evaluating the use of botulinum toxin for the prevention of POAF was the phase 2 randomized, double-blind, placebo-controlled NOVA trial (Neurotoxin for the Prevention of Post-Operative Atrial Fibrillation). The study enrolled 323 patients undergoing cardiac surgery, primarily CABG, valve surgery, or combined procedures. Patients were randomly assigned to one of three groups receiving either 125 units of botulinum toxin type A, 250 units (50 U/ml), or placebo, administered intraoperatively into the EAT. Randomization was stratified according to type of surgery (with or without valve intervention) and age (<65 or ≥65 years) [32].

The primary endpoint was the incidence of POAF lasting at least 30 seconds within 30 days post-surgery. POAF occurred in 46% of patients in the placebo group, 47% in the 250 U group, and 36% in those receiving 125 U. Although these differences did not reach statistical significance in the overall population, post hoc analyses demonstrated benefits in patients aged ≥65 years and in those undergoing isolated CABG. The 125 U dose was also associated with lower levels of inflammatory biomarkers (hsCRP, IL-6) and reduced rates of interventions and rehospitalizations within 30 days.

No significant adverse events or deterioration of pulmonary function were observed. The findings suggest the existence of an optimal therapeutic dose and a potential mechanism of action of botulinum toxin—through autonomic nervous system modulation and reduction of the inflammatory response. The lack of efficacy at the higher dose (250 U) may be related to excessive suppression of parasympathetic activity [32,33].

Phase 3 trials are currently underway to confirm the results of previous studies. One of them is the randomized, double-blind BOTAF trial (Botulinum Toxin for the Prevention of Postoperative Atrial Fibrillation), which evaluates the efficacy and safety of botulinum toxin Xeomin® in the prevention of POAF among 220 patients undergoing CABG or valve surgery. The study began in 2019, with completion expected in the second half of 2025. The primary objective is to assess the effect of intraoperative injection of the toxin directly into the EAT on the incidence of POAF and the safety profile of the therapy [34,35].

At present, no therapy has been approved by FDA for the prevention of POAF. The available study results on botulinum toxin suggest potential clinical benefits in selected patient groups, particularly in those undergoing isolated CABG and in patients aged ≥65 years. These encouraging findings provide the basis for further large-scale, registration trials [31,32,33,34].

Study	NOVA	Pokushalov et al., 2014	BOTAF
Year	2023	2014	2019–2025
Number of patients	323	60	220
Type of surgery	CABG / valve / combined	CABG	CABG / valve
BoNT dose	125 U / 250 U	200 U	n/a
Incidence of POAF (BoNT group)	0,36	0,07	n/a
Incidence of POAF (placebo group)	0,46	0,3	n/a
Follow-up period	30 days	3 years	Until Sept 1, 2025

Limitations and Perspectives of Use

Although clinical results are encouraging, the application of botulinum toxin for POAF prevention is limited by the need for intraoperative delivery directly into the EAT. Because of its invasive character, this approach is currently restricted to patients undergoing open cardiac procedures, such as CABG or valve surgery. Future research should focus on identifying patient subgroups most likely to benefit from this therapy, particularly those with large EAT volumes, chronic inflammation, or elevated POAF risk.

Conclusions

The administration of botulinum toxin type A (BoNT-A) for the prevention of POAF represents an innovative therapeutic strategy based on temporary neuromodulation of the autonomic nervous system. Current studies indicate its effectiveness in reducing the incidence of POAF, particularly in patients over 65 years of age and those undergoing isolated CABG.

From a clinical perspective, BoNT-A may in the future become a valuable adjunct to current prophylactic strategies, particularly in high-risk patients. Its potential applications could also extend to other autonomically mediated arrhythmias, such as paroxysmal atrial fibrillation and supraventricular tachyarrhythmias. However, the invasive nature of the procedure remains the main barrier, currently limiting its broader clinical implementation.

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resources: Anna Kaźmierska
data curation: Maciej Kaźmierski
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visualization: Anna Kaźmierska
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