Use of botulinum toxin in the management of radiotherapy side effects

Využití botulotoxinu při léčbě nežádoucích účinků radioterapie

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Summary

Background: Many experimental and clinical studies are conducted to investigate the effects of various applications of botulinum toxin (BTx) in the treatment of radiation related side effects. There are no studies that show clear results about the positive and negative effects of its active clinical use in the long run, and discussions are ongoing. In addition, there is a need for various researches about how BTx can be used and how long it can be used, and the side effects it may cause. BTx-A, which is one of the options in the treatment of side effects that will occur due to radiotherapy, is an effective and safe option. Applying BTx injection to the right place with specific injection methods increases the effectiveness and safety of the treatment. ***Purpose:*** It has been investigated whether BTx will be a potential tool to perfect the esthetic and functional results in reducing the chronic side effects associated with radiotherapy.

Key words

radiotherapy – botulinum toxin – side effects – treatment

Souhrn

Východiska: Mnohé experimentální a klinické studie jsou prováděny s cílem prozkoumat účinky různých aplikací botulotoxinu (BTx) při léčbě nežádoucích účinků radioterapie. Neexistují žádné studie, které by ukazovaly jasné výsledky ohledně jeho pozitivních a negativních účinků při aktivním klinickém využití v dlouhodobém měřítku a na toto téma probíhají diskuze. Navíc je třeba prozkoumat, jakým způsobem a jak dlouho lze BTx používat a jaké může vyvolat nežádoucí účinky. Účinnou a bezpečnou možností při léčbě nežádoucích účinků vyvolaných radioterapií je BTx-A. Aplikace injekce BTx do správného místa určitým způsobem vpichu zvyšuje účinnost a bezpečnost léčby. ***Cíl:*** Bylo zkoumáno, zda BTx bude potenciálním nástrojem pro dosažení dokonalých estetických a funkčních výsledků při snižování chronických nežádoucích účinků vyvolaných radioterapií.

Klíčová slova

radioterapie – botulotoxin – nežádoucí účinky – léčba

The authors declare that they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Submitted/Obdrženo: 30. 12. 2021
Accepted/Přijato: 30. 8. 2022

doi: 10.48095/ccko2023348

Introduction

Side effects due to radiotherapy (RT) create difficulties in the quality of life by revealing difficulties in patients' daily activities. With the development of diagnosis and treatment methods, great progress has been made in the solution of these problems. In its treatment, conservative and surgical treatment methods are applied. The applied surgery and the effectiveness of the treatment are evaluated with functional status, patient satisfaction, subjective pain notification, and imaging methods such as MRI and CT. Conservative treatments are mostly symptomatic and cannot cure. Therefore, the search for new curative treatment strategy continues. For this purpose, many experimental and clinical studies are conducted to investigate the effects of various applications in the treatment of radiation related side effects [1–5]. In recent years, botulinum toxin (BTx) A, which has been widely used in many areas, has become a subject of research in the treatment of toxicity. In many studies and case reports conducted until now, BTx has been reported to be superior to other pharmacological drugs in terms of both efficacy and few side effects [3–8].

The toxin discovered as a result of paralysis after food poisoning at the end of the 19th century has been used in many fields of medicine today. BTx is a protein produced by *Clostridium botulinum*, a gram-positive, anaerobic bacteria. Eight serotypes, namely A, B, C1, C2, D, E, F and G, were identified immunologically. The toxin is mainly in the neuromuscular junction; it prevents the release of acetylcholine in the presynaptic ends of cholinergic, sympathetic and parasympathetic neurons. As a result, BTx acts by inhibiting signal transmission in the peripheral motor, sympathetic and parasympathetic nervous systems [9,10].

In this article, it has been investigated whether BTx will be a potential tool to perfect the esthetic and functional results in reducing the chronic side effects associated with radiotherapy.

BTx's history

In 1817, Dr. Justinus Kerner is the first to clinically identify BTx poisoning [11]. Then Prof. van Ermengen reported that BTx caused paralysis in the muscles and caused death by anaerobic spore bacillus botulinus, which is the source of this toxin, and has changed to Clostridium botulinum in the course of time [12].The first antiserum for botulism was developed by W. Kemper in 1897. In 1949, Burgen defined the mechanism of action of BTx. It was tested in animals by Scott in 1973. Five years later, the first pilot study was carried out [10]. In 1989, Food and Drug Administration approved for the treatment of strabismus, hemifacial spasm and blepharospasm [14]. In 1990, Jean Carruthers and Alastair Carruthers were first used to remove facial wrinkles. In 2007, Van Beek found that the patient with the Reynaud phenomenon had a marked decrease in pain after BTx injection, improvement in fingertip ulcers and a decrease in attack frequency [15]. In 2009, Neumeister reported that BTx therapy on ischemic fingers reduced pain and corrected vascularity. In the last 20 years, it has started to be preferred in many areas of medicine [10,14,15].

BTx's mechanism of action

It is a polypeptide molecule consisting of a light and heavy chain with a molecular weight of 150 kD. The light chain contains zinc-dependent metalloproteinase enzyme activity linked by heat-sensitive disulfide bridges. With this protease, the toxin is converted into its active form. The toxin motor is taken to the nerve through endocytosis to the nerve, and it connects to the membrane complex of SNARE (Soluble N-ethylmaleimide sensitive fusion protein Attachment REceptor), which is involved in the calcium-dependent exocytosis of acetylcholine in the light chain cholinergic nerve terminal, and the action potential in the motor endplate cannot be formed as a result of cholinergic transmission. BTx has 8 serotypes, A, B, C1, C2, D, E, F and G, each showing its effect on a different SNARE protein. Although each has a different antigenic profile and biochemical effects, the pharmacological effects are all the same. BTX-A is known as the strongest subtype [16].

BTx shows its effect through 3 mechanisms: 1) eliminating the reactionary forces on the healing wound by inhibiting muscle contraction in the surrounding tissues [17]; 2) inhibition of fibroblast apoptosis and inhibition of proliferation, balancing cell dynamics and reducing collagen production [18]; 3) reducing fibroblast and myofibroblast efficacy with transforming growth factor (TGF) beta-1 and connective tissue growth factor inhibition [19].

BTx-A inhibits the release of acetylcholine in motor end plates in muscle tissue, causing paralysis in muscle tissue. Thus, external forces that will deform muscle repair are inhibited. In addition to the facial rejuvenation effect with paralysis in BTx mimic muscles, it also has different effects such as reducing scar tissue and facilitating tissue expansion [15,19]. In addition to performing vasodilation as a result of BTx-A suppressing sympathetic neurons in the skin flaps, there are studies in the literature that increase the blood flow and viability of the flap by triggering angiogenesis by increasing the release of mediators such as vascular endothelial growth factor and CD31 [20]. In addition, anti-inflammatory properties of BTx have been reported in the literature [21]. Moreover, animal experiments have been shown to reduce hypertrophic scar formation by inhibiting TGF beta-1 release in the region where BTx-A is applied [18].

It is injected into carefully selected muscles or glands in clinical use. Its effect is most seen in the injected area. The diffusion capacity of BTx depends on the subtype of the toxin, the characteristics of the area where it is applied and the dose administered. After BTx application, the activity of botox in the cell starts and it takes 3–5 days to see its clinical effects. Its maximum effect peaked in about 7–14 days. The chemodenervation state begins to return approx. 4–8 weeks when the axons sprout and provide reinnervation. The time it took for reinnervation to occur and to re-release acetylcholine was reported to be 91 days in studies [10,17].

Treatment indications and new applications of BTx

BTx, which has a very important place in medicine, was discovered in the 18th and

19th centuries. The toxin's mechanism of action was understood only in the 20th century. Following successful applications in the treatment of strabismus, it has been used in the treatment of many neurological and ophthalmic diseases, cosmetics, general surgery, maxillofacial surgery, orthopedics and thoracic surgery, dermatology, otolaryngology, pain clinics, pediatrics, rehabilitation units and urology. O'Reilly et al. reported that after the use of BTx-A in the treatment of axillary hydradenitis, regional lesions disappeared and they did not see recurrence within 10 months [22]. Chenwang et al. investigated the BTx A application in muscle-skin flap expansion and found that it reduced resistance in the flap, increased the enlarged area, and reduced flap contraction [23]. Clemens et al. investigated the effect of BTx-A on rat femoral vessel diameters and the success of anastomoses. For this purpose, it was shown that vasospasm and thrombosis were reduced, dilatation of the veins and arteries, and anastomosis was performed in a shorter period of time in rats that received 10 units of BTX-A perivascular 5 days before surgery [24]. In another study, BTx-A was applied to prevent pectoral muscle spasm following subpectoral implant placement. It was stated that this method can be preferred to neurectomy because the patients experience a painless postoperative period, better cosmetic results and cause a reversible denervation [25]. BTx-A flexor tendon repair was applied to the muscle origins of patients who underwent repair and it was reported that tendon rupture rates decreased [26]. In order to prevent enlargement of scars on the face, BTx-A injection to wounded lips has been reported to be beneficial in wound healing [27] and in preventing a hypertrophic scar formation [28].

In many studies, he argued that the use of BTx-A is practical and can be used in the clinic. Various hyperkinetic-dystonic disorders, achalasia, spasmodic dysphonia, anal fissure, parkinson tremor, oddi sphincter spasm, synkinesia, hyperhidrosis, migraine-type headache, tetanus, spasticity, nystagmus, stuttering, spastic bladder, facial wrinkles, perioperative and post-operative pain control, hypersalivation and paralysis of the geniohyoid muscle are used in the treatment of diseases [6–28].

Side effects and drug interaction related to BTx

After percutaneous injection, local pain, edema, ecchymosis, bleeding and infection may occur in that area. A general malaise, fatigue, headache, and flu-like syndrome have also been reported. Dry mouth sensation, dry skin, flaking, temporary hyperesthesia can be seen. Some advantages of botox injection; ease of application, no sensory impairment, low systemic side effects, and reversible effects in 2–3 months. Being expensive and the possibility of developing antibodies against toxins are some disadvantages. Biological tolerance may develop in repeated injections. Therefore, it requires applications that are repeated at regular intervals. In human and animal studies, immunological and carcinogenic side effects were not detected. Drugs such as aminoglycosides (gentamicin), cyclosporin, D-penicillamine, curarine nondepolarizing blockers, succinylcholine, aminocinolones, quinidine, magnesium sulfate and linkosamide increase the effects of BTx-A. Aminoquinolones such as chloroquine and hydrochloroquine interact with BTx-A in the cell and inhibit the effect of toxin [9–17].

Use of BTx in radiotherapy

When the literature is examined, it is seen that BTx is applied in the treatment of toxicity due to RT. Generally, clinical studies involving the effect of BTx on head and neck tumors have been conducted. In a clinical study conducted by Mailly et al. on 16 patients, they looked at the effectiveness of BTx-A, where they applied a single dose in head and neck pain caused by radiation. When the pain score was evaluated before and after the treatment, they stated that 11 patients completely passed the pain and this difference was significant. As a result, BTx-A has been reported to be an effective treatment for head and neck pain caused by radiation [2]. In another clinical study, it was reported that pain was relieved after BTx injection into the sternocleidomastoid muscles in the painful spasm of the neck muscles in patients undergoing primary and adjuvant radiotherapy due to a head and neck tumor [3]. In another similar clinical study, it has been reported that BTx can be recommended in nasopharyngeal cancer to correct diplopia due to radiotherapy and/or chemotherapy [7]. Melville et al. reported that sialaocele and fistula healed in 3 patients who applied BTx-A after buccal squamous cell carcinoma after tumor excision, neck dissection and flap reconstruction [29]. Lidocaine and BTx injections applied percutaneously in patients after total laryngectomy and trachea esophageal puncture have been reported to be successful in aponic treatment with minimum complications [30]. The effectiveness of upper esophageal sphincter dilatation, cricopharyngeus myotomy and intramuscular BTx (botox) injection in patients with head and neck cancer was evaluated in a review. The success rate of dilation was found to be 42–100%, myotomy 27–90% and 65% in the botox group. They concluded that, due to lack of consistency between studies, excessive standardization is needed to guide clinical practice [4]. In a study by Salazar et al. in patients with nasopharyngeal cancer who developed oromandibular dystonia after radiotherapy, BTx-A (total dose 100 IU) was applied to both masseter muscles in patients who developed oromandibular dystonia. On the 4th day, they stated that their complaints completely subsided and that BTx was effective for 3 months [31]. They stated that in patients with head and neck cancer who developed neck contracture after radiosurgery, the effect was observed 6 days after the BTx injection applied to the sternocleidomastoid or pectoralis major flap, and this effect lasted for 19 days. As a result, it has been emphasized that studies are needed to determine the injection sites and dose [32].

There are studies in the literature about the toxicity reduction feature of BTx applied before radiotherapy. In the prospective, randomized, placebo-controlled, double-blind phase I clinical trial, BTx or sodium chloride injection was

applied to the submandibular glands before treatment in patients with radiotherapy. There was no difference between the groups in the analysis of salivary gland function and scintigraphic data. It has been reported that BTx can be used safely with chemoradiotherapy, but studies investigating the efficacy and timing of the BTx injection to assess its effectiveness [8]. Wong and colleagues looked at the efficacy and safety of BTx injection in the treatment of strabismus due to nasopharyngeal cancer. They had BTx injection before chemoradiotherapy. Patients who continued with diplopia also received additional BTx injection during treatment. They stated that BTx injection significantly reduced strabismus [6]. In a recent study, BTx was shown to increase the effect of radiotherapy and chemotherapy by opening the vessels in the tumor microenvironment instead of a direct cytotoxic effect on tumor cells [1].

There are limited number of studies on the role of BTx in treatment with radiotherapy-related toxicity in other cancers of the region, except for the head and neck tumors. In a review that evaluates the treatment efficacy of BTx injection in hemorrhagic cystitis after radiotherapy in gynecological tumors, it is stated that BTx causes local muscle paralysis and increases bladder capacity by preventing the release of neurotransmitter acetylcholine in neuromuscular junctions. It has also been reported to act by acting as an anti-inflammatory drug by suppressing EP4 receptors and cyclooxygenase-2. As a result, it was emphasized that hemorrhage may be a promising treatment for BTx in cystitis [5]. In the phase I/II study conducted by Vuong et al., BTx-A was applied at a dose level of 100 units to reduce acute proctitis in patients who received neoadjuvant brachytherapy due to rectal cancer. They stated that BTx reduces symptoms of rectal burning/tenesmus and pain [33]. In another clinical study, it has been reported that onabotulinum toxin A (20–100 units) applied to focal pain regions significantly reduces pain and improves quality of life in cancer pain resistant to treatment after radiotherapy and/or surgery [34].

Conclusion

BTx-A, which is one of the options in the treatment of side effects that will occur or occur due to RT, is an effective and safe option. Applying BTx injection to the right place with specific injection methods increases the effectiveness and safety of the treatment. However, there are no studies that show clear results about the positive and negative effects of active clinical use in the long run, and discussions are ongoing. In addition, there is a need for various researches about how long BTx can be used and how long it can be used, and the side effects it may cause.

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