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Clinical Importance of Botulinum Toxin Applications in Cervical Dystonia

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Abstract

Objective: To compile and reveal the clinical importance of botulinum toxin applications in cervical dystonia. Materials and Methods: When we searched the PUBMED database with the keywords "cervical dystonia botox", 472 studies were obtained and 104 publications were found when clinical studies were selected. Results: While 38 of the 472 studies in the literature belong to the last ten years, when the options for accessing the full text were filtered, 181 studies were carried out in the last 10 years and the full text of 56 of them could be accessed. Only 9 of these are clinical trials. When the full-text clinical study was selected, 17 studies were obtained, 9 of which were conducted in the last ten years. Conclusion: Cervical dystonia is one of the most common application areas of botox apart from cosmetic use. There are not many studies on physiotherapy in cervical dystonia yet. As a result of the literature review, we think that although botulinum toxin is one of the best treatment options for cervical dystonia, adding physiotherapy to the treatment process will yield better results.

Keywords: botox; botulinum toxin; cervical dystonia

1. Introduction

Botulinum toxin is a neurotoxin produced by *Clostridium botulinum*, a gram (+), anaerobic bacterium. The toxin causes loose type paralysis in striated muscles. There are 8 serologically distinguishable serotypes of the toxin, which are types A, B, C1, C2, D, E, F and G. Today, only the most effective type A is used [1]. After more than thirty years of clinical use, it has become a multi-purpose drug used in every field of medicine [2]. When we searched the PUBMED database with the keywords "cervical dystonia, botox and botulinum toxin", 472 studies were obtained and 104 publications were found when clinical studies were selected. While 38 of these studies belong to the last ten years, when the options for accessing the full text were filtered, 181 studies were conducted in the last 10 years, and the full text of 56 of them could be accessed. Only 9 of these are clinical trials. When the full-text clinical study was selected, 17 studies were obtained, 9 of which were conducted in the last ten years.

2. History of Botulinum Toxin

In the twentieth century, BTX has been used as a biological weapon by many countries. Although many countries have signed the "Biological and Toxic Weapons Convention", research on biological weapons has stopped [3]. Foodborne botulism was first described in 1820 by the German physician and poet Justinus Kerner [4]. In 1989, in patients older than 12 years; approved for the treatment of cervical dystonia [5]. Botulinum toxin is a protein produced by the anaerobic bacterium *clostridium botulinum*. Müller was the first to use the term botulism (Latin for sausage = botulus) in 1870 and explained the effects of sausage poisoning. The culprit bacterium was found in 1895. While this anaerobic bacterium, which was previously isolated from food, was called *Bacillus botulinus*, it was later named *clostridium botulinum* [6].

3. Mechanism of Botox Effect

BoNT-type A consists of two polypeptide chains, 100 kDa heavy and 50 kDa light, linked by disulfide bonds. Light chain is a zinc-dependent protease enzyme, it acts on fusion proteins (SNAP-25, syntaxin, snapto brevin) that enable acetylcholine vesicles to anchor to the presynaptic membrane at the neuromuscular junction [7]. When BoNT-type A is injected into muscle, it is taken up by endocytosis from the presynaptic nerve end at the neuromuscular junction, inhibits acetylcholine release by affecting fusion proteins, this chemical denervation leads to loose paralysis in the muscle [8]. Generally, the effect reaches its maximum in 2 weeks, lasts for an average of 3 months, and complete recovery occurs in 4-6 months with the completion of reinnervation. The mouse unit (MU, LD50, U) is used to measure BoNT-type A activity. 1 "mouse unit" (MU) activity is defined as the dose that kills

50% of the mice with an intraperitoneal BT injection of 18-20 grams of Webster type mice [9]. They are diluted with isotonic saline solution and administered intramuscularly. Injections made at short intervals (less than 3 months) and in high doses can lead to the development of antibodies and loss of efficacy, so they should be avoided [10].

4. Side Effects

The main side effects of BoNT-type A are inappropriate muscle and/or undesirable weakness caused by the effect of the toxin and allergic reactions caused by its chemical structure. Common side effects; Temporary weakness in the injected or adjacent muscles. Pain at the injection site, itching, redness, ecchymosis (periorbital), dysphagia, dry mouth and eyes, drooping eyelids and eyebrows. In addition, skin rash due to allergic reaction, angioedema, flu-like picture, generalized botulism findings (fatigue, respiratory distress, dysphagia) may also be seen [10].

5. Usage Areas

Usage Areas are listed below[11, 12, 13, 14, 15, 16, 17, 18, 19].

- 1) Facial Aesthetics Applications; Glabellar Complex and Forehead Wrinkles, Lateral Canthal Wrinkles (Crow's Feet), Nasal Back Applications (Rabbit Lines), Nose lift, Perioral Lines (Smoker's Line), Marionette Lines (from m. depressor anguli oris), Gummy Smile, Masseter Hypertrophy, Plastic Tapes

- 2) Focal Dystonias; Blepharospasm, Extremity dystonias, Oromandibular dystonia, Cervical dystonia, Orolingual dystonia, Laryngeal dystonia, Trunkaldystonia

- 3) Involuntary Movement Disorders; Myokimias and synkinesia, Tremor, Hemifacial spasm, Tics, Myoclonus.

- 4) In Autonomic Nervous System Disorders; Axillary and palmar hyperhidrosis, sialorrhea, hyperlacrimation, allergic rhinitis, auriculotemporal syndrome.

- 5) Muscle spasm; Chronic low back pain, tension-type headache, migraine, myofascial pain syndrome.

- 6) Strabismus.

- 7) Spasticity; stroke, cerebral palsy, multiple sclerosis, brain and spinal cord injuries.

- 8) Smooth muscle hypertrophy; Detrusor-sphincter dyssynergia, after hemorrhoidectomy, dysfunction of the oddi sphincter, cardia achalasia, anal fissures, benign prostatic hypertrophy.

- 9) Applications to the stomach muscles to prevent obesity. Botulinum toxin is the first and most effective treatment option in cervical dystonia [20, 21]. If we examine the studies on this subject in the literature, Kocaman et al. In their 2009 study, they examined the changes in muscle activation pattern before and after botulinum toxin administration in patients with idiopathic cervical dystonia. Nine cervical dystonia patients, 5 women and 4 men, aged between 32-65 years, were

included in the study, and they applied the average total dose of Botox® (minimum 100, maximum 290 U) used in a single session as 160 U. They found that 88.8% of the patients showed subjective improvement and an average of 55% improvement in head posture [22]. Akin et al. In their study conducted in 2012, they examined 118 cervical dystonia cases who received botulinum toxin treatment. In a total of 430 sessions, an average of 153.4 units of botulinum toxin was administered to the patients. The patients felt the first recovery at a rate of 58.7% and after about 8.7 days, and the botulinum toxin effect ended after an average of 2.9 months. The patients reported a mean recovery rate of 57.5% on the visual analog scale. As a result of the injections, no side effects were detected in 72.3%, difficulty in swallowing in 8.3%, neck pain in 7.7%, weakness in the neck and falling forward in 5.1%, dystonia in 3.2%. deformation and dry mouth were found in 2.2% of them. In patients who were administered Dysport, the mean improvement was 44.1%, the duration of efficacy was 2.3 months, and the incidence of side effects was 62.5% [23]. The first-line therapy for cervical dystonia (CD) is botulinum toxin type A (BoNT-A), which has been established as a highly effective and well tolerated therapy. However, the clinical application of this therapy is complex and difficult. About 20% of patients discontinue treatment due to treatment failure, side effects and other reasons. Among the issues still to be clarified is the optimal dosage amount. The generally accepted standard for intervals between BoNT-A injections is ≥ 12 weeks; However, this standard is based on the methodology of baseline trials for BoNT-A products, rather than evidence of optimal fit compared to other ranges. According to some retrospective reviews, observational studies of BoNT-A used in clinical practice support the use of dosage intervals of ≥ 12 weeks, but it is unclear how the need for reinjection was determined in these studies. In contrast, a prospective dose range trial in which patients were allowed to request reinjections as early as 8 weeks showed that approximately half of patients receiving abobotulinumtoxinA at the currently recommended dose of 500 U requested reinjections at 8 weeks. In addition, results from an open-label, 68-week extension phase of the pivotal study of incobotulinumtoxinA showed that 47.1% of patients received reinjections at ≤ 12 weeks. Ongoing studies such as the Cervical Dystonia Patient Registry for Monitoring BOTOX® Efficacy (CD PROBE) may help clarify this question regarding optimal dosage ranges for BoNT-A in CD [24].

6. Cervical Dystonia and Botulinum Toxin Applications

Apart from the use of botox for cosmetic purposes, it is often preferred for the treatment of diseases such as cervical dystonia, severe primary axillary hyperhidrosis, strabismus, neurogenic detrusor overactivity, chronic migraine, upper extremity spasticity and blepharospasm. Botox has a wide variety of therapeutic uses, and patients receiving this treatment may occasionally experience local or more widespread autonomic symptoms. Rouientan et al. In their study in 2019, they examined a rare complication seen in botox injection. The 22-year-old male they

reported received Botox for axillary hyperhidrosis, and most of the general complications of botulinum toxin appeared two weeks later. The patient regularly applied for the treatment of axillary hyperhidrosis with 150 IU Botox every 3-4 months. While there were no complications at the end of the first three injections, instead of 50 units of three bottles of Botox, 100 units of three bottles of Botox were used in the last session. About two weeks after the injection, the patient began to complain of malaise, weakness, vision problems, diplopia, dysphagia, and a feeling of suffocation at night. He visited the ophthalmologist and an asthma and allergist. After performing a normal ECG-CXR, the physician diagnosed eosinophilic esophagitis and referred the patient to a gastroenterologist for further evaluation. After endoscopy and biopsy, all reports and results were found to be normal in pathology examination. A Botox injection complication was diagnosed. As a result, they stated that the use of three out of 100 botox for the treatment of hyperhidrosis may cause local and systemic side effects [24].

Yi et al. In 2018, they conducted a study of 16 adults with dyskinetic cerebral palsy over 20 years of age who had been clinically diagnosed with cervical dystonia for more than one year. The study evaluated the efficacy and safety of injecting botulinum toxin A (BoNT-A) into the neck muscles. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used in the study. After four weeks of experiments, BoNT-A injections showed significant improvement in TWSTRS total scores compared to saline injections ($p=0.0286$). At the end of 12 weeks, BoNT-A injections led to greater improvements in TWSTRS total scores than saline injections, but did not achieve statistical significance ($p=0.0783$). They found that dysphagia occurred in three of 16 patients: two after BoNT-A and one after saline [25].

Botulinum toxin (BoNT) injections in dystonic muscles are the treatment of choice for Cervical Dystonia (CD), but proper identification of dystonic muscles remains a challenge. Cumulative distribution functions (CDFs) of dystonic muscles showed increased values of CDF10 representing increased autospectral powers from 3 to 10 Hz relative to power from 3 to 32 Hz. In previous studies, 8–14 Hz autospectral power was found to be decreased in electromyography (EMG) of the splenius muscles in CD patients. Nijmeijer et al. In their study in 2017, they evaluated both methods and investigated the effects of botulinum toxin. Intramuscular EMG recordings were obtained from the splenius, semispinalis, and sternocleidomastoid muscles during standard isometric work in 4 patients with CD treated with pure BoNT, 12 patients treated with BoNT, and 8 healthy controls. BoNT-treated patients were remeasured at 4–7 weeks and 11–15 weeks after their last BoNT injection. They found that in CD patients, the autospectral power of 8–14 Hz was significantly reduced in the splenius muscles, but not in the semispinalis and sternocleidomastoid muscles compared to healthy controls. They found increased CDF10 values in all CD patient muscles based on their evaluation of CDF10 analysis, which was superior in demonstrating subtle autospectral changes. They also stated that these results did not change significantly after BoNT injections [26].

Huang et al. In their study conducted in 2015, they analyzed the effective-

ness of ultrasound-guided local injection of botulinum toxin type A treatment with orthopedic joint support in patients with cervical dystonia. They included 105 patients with cervical dystonia in the study and divided them into three groups: those who received medical treatment, those who received botulinum toxin treatment with ultrasound therapy, and those who received botulinum toxin treatment under ultrasound treatment with orthopedic joint splint. Tsui scale and Spitzer quality of life index were applied to evaluate spasm, quality of life and treatment effectiveness. Tsui scale and Spitzer quality of life index scores were evaluated at the end of one month, three months, and six months. The difference in Tsui and Spitzer scores before and after medical treatment was not statistically significant. A significant difference was found between the Tsui and Spitzer scores between the groups that received botulinum toxin therapy with ultrasound therapy and the groups that received botulinum toxin therapy with orthopedic joint splint and ultrasound therapy [27].

Jankovic et al. In their study conducted in 2015, they investigated the effectiveness of botox treatment in patients diagnosed with cervical dystonia by examining patient records. The records of patients who did not apply botox for 16 weeks or who have just been applied were included in the study. They administered three doses of treatment and compared the results of these treatments. They examined 1046 individuals with a mean age of 58.0 ± 14.7 years, 74.4% of whom were women. The mean dose was 189.8 ± 87.1 U, with mean treatment intervals of 14.6 and 15.1/week. Participants were assessed using the Average Toronto Western Spasmodic Torticollis Rating Scale and found that the 479 participants who completed all assessments had a baseline mean score of 39.2 to 27.1. They stated that this was a sign of significant improvement. Overall, 26.2% of participants reported different events, including muscle weakness (7.0%) and dysphagia (6.4%). In conclusion, they showed significant improvement in clinical grades and excellent tolerability of cervical dystonia following botulinumtoxinA treatment [28].

Yun et al. In their study conducted in 2015, they investigated the effectiveness of Dysport and Botox in a ratio of 2.5:1 in cervical dystonia. The study was designed as double-blind. A Dysport/Botox ratio of less than 3:1 has been widely used in other focal movement disorders in addition to the treatment of cervical dystonia and has been recommended as the dose with positive response. In the study, patients were randomly selected and followed up 16 weeks after their first treatment with Dysport or Botox. In the primary outcome assessment, they examined the change between the baseline value on the Tsui scale and the value 1 month after each injection. A total of 103 patients were included in the study, but 94 of them completed the study. Examining changes in the mean on the Tsui scale and at 4 weeks after each injection, they found no significant difference (4.0 ± 3.9 points for Dysport treatment, 4.8 ± 4.1 points for Botox, $P = 0.091$). When they compared the mean change of the Toronto western spasmodic torticollis rating scale score, they found no significant difference between the two treatments [29].

Mordin et al. In a study they conducted in Russia and the USA in 2014, they studied the factors affecting the health-related quality of life of patients with cer-

vical dystonia and the effect of treatment with botulinum toxin A (Dysport). They planned the study as a randomized, double-blind, placebo-controlled study. They selected patients from those diagnosed with cervical dystonia with symptoms for at least 18 months and used the Toronto Western Spasmodic Torticollis Scale (TW-STRS) for assessment. The patients received 500 U botulinumtoxin A (n = 55) and the control group received placebo (n = 61). While they found a significant increase in complaints in patients with cervical dystonia who received placebo compared to the US norms, they stated that patients treated with botulinumtoxin A improved more than patients with placebo in the areas of physical functionality, physical role, physical pain, general health, and sense of role [30].

Evidente et al. In their study in 2014, they investigated the efficacy of incobotulinumtoxinA (Xeomin®) injected according to patient needs for blepharospasm or cervical dystonia. Typically, botulinum toxin injections for blepharospasm or cervical dystonia are administered at approximately 3-month intervals; stated that shorter intervals may cause side effects and increase the risk of developing neutralizing antibodies. Post-hoc analyzes in this study examined flexible incobotulinumtoxinA (Xeomin®) injection intervals (6-20 weeks) in patients with blepharospasm or cervical dystonia. In the cervical dystonia study, they used incobotulinumtoxin A 120 U, 240 U, or placebo for initial therapy at a fixed dosage, followed by randomization to 120 U or 240 U for the extension period. It was studied in 207 of 461 (44.9%) treatment cycles for blepharospasm and 369 of 821 (44.9%) treatment cycles for cervical dystonia. The most common side effects in patients treated for blepharospasm were ptosis and dry eyes, while dysphagia and neck pain were noted in patients with cervical dystonia [24].

Van Den Dool et al. In their 2013 study, they investigated the effectiveness of a standard physical therapy program in patients with cervical dystonia. In a multicenter, single-blind, randomized controlled study, 100 patients with cervical dystonia were studied. As adjunct therapy to botulinum toxin injections, a standardized physical therapy compared to normal physical therapy was administered. The Toronto Western Spasmodic Torticollis Rating Scale was used for evaluations in the study. In the primary results, insufficiency in daily functioning was observed, which corresponds to the disability subscale of the scale used. In addition pain, severity of dystonia, active range of motion of the head, quality of life, anxiety, depression, and economic status were also evaluated. Evaluations were carried out at 6 months and 12 months. As a result, they found that the effect of Botox prevented pain and doing daily life tasks less than the classical treatment method. They also found that additional treatment alone increased the effect of botox even more [31].

Long-term management of cervical dystonia includes repeated injections of botulinum toxin at approximately 3-month intervals. Coulon analyzed the clinical need and safety of flexible injection intervals with Incobotulinumtoxin A (Xeomin®, NT 201), a purified botulinum toxin type A that does not contain accessory (complexing) proteins. The study was planned as randomized, double-blind, placebo-controlled. The common opinions of the participants and physicians about the

need and a total score of 20 from the Toronto Western Spasmodic Torticollis Rating Scale were accepted as criteria for repetition of botox treatment. All standard safety assessments have been made and applications have been carried out. Two hundred and fourteen subjects entered the extension period (120 U dose group, n = 103; 240U dose group, n = 111). A total of 821 injections of incobotulinumtoxin A were administered, 369 (44.9%) at 6-11-week intervals and 452 (55.1%) at 12-20-week intervals. In conclusion, incobotulinumtoxin A (Xeomin®), injected at flexible intervals according to clinical needs, was found to be effective and well tolerated in the long-term management of cervical dystonia [32].

In their 2013 study, Evidente et al. conducted a randomized, double-blind study to investigate the effect of repeated incobotulinumtoxinA (Xeomin®) on cervical dystonia. They stated that incobotulinumtoxinA (Xeomin®, NT 201), a preparation that does not contain an accessory (complexing) protein, has demonstrated efficacy and safety comparable to OnabotulinumtoxinA in the treatment of cervical dystonia (CD). They established a procedure to administer 240 U or 120 U incobotulinumtoxinA (*leq*5 injections) at flexible intervals of at least 6 weeks with a repeated dose of *leq*68 weeks, after a 20-week placebo-controlled, randomized, double-blind, single-dose main period. They used the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) as a tool to evaluate the results and recorded the side effects. Of the 219 participants who completed the study, 214 were randomized to receive incobotulinumtoxinA 240 U (n = 111) or 120 U (n = 103) during the extension period; 169 people completed the extension period, while 90 received five injection sessions. They found statistically and clinically significant improvements in TWSTRS- scores for both incobotulinumtoxinA doses. They noted the most frequently reported side effect as dysphagia [33].

Charles et al. In their study in 2012, they conducted a randomized, double-blind, placebo-controlled study to investigate the efficacy, tolerability and immunogenicity of botulinumtoxin A in patients with cervical dystonia. They divided 170 cervical dystonia patients with an average age of 55 from 22 centers in the USA and 1 center from Canada as 88 people who received botox and 82 people who were in the placebo group. In the group receiving placebo, rhinitis and treatment-related dysphagia were reported significantly more frequently with botulinumtoxin than with placebo. As a result, botulinumtoxinA was better tolerated than placebo for the treatment of cervical dystonia [34].

Comella et al. In their study conducted in 2011, they investigated the efficacy and safety of botulinumneurotoxin type A botox treatment in patients with cervical dystonia. IncobotulinumtoxinA differs from existing formulations in that it does not have ancillary proteins. In practice, they found that incobotulinumtoxinA 1:1 dose regimen had an equivalent effect against onabotulinumtoxinA for the treatment of cervical dystonia. In this study, they conducted a prospective, double-blind, randomized, placebo-controlled, multicenter clinical trial comparing the safety and efficacy of incobotulinumtoxin A (120 U, 240 U; MerzPharmaceuticals) in patients with cervical dystonia. Using the Toronto Western Spasmodic Torticollis Scoring Scale (TWSTRS), the period from the start of treatment to 4

weeks was evaluated and side effects were also followed. 66% of the participants (n=233) were female, with a mean age of 52.8 years and had cervical dystonia for an average of 51.9 months. They found that incobotulinumtoxinA induced TWSTRS-Totalscos significantly improved from baseline to week 4 compared to placebo (placebo = -2.2; 120 U = -9.9 and 240 U = -10.9; 240 U vs. placebo pb0.001 and 120 U vs. placebo pb0.001). The most frequently reported side effects in the incobotulinumtoxinA groups were dysphagia, neck pain, and muscle weakness, which was generally mild. As a result, they found that incobotulinumtoxinA (120 U or 230 U doses) is a safe and effective treatment method for cervical dystonia [35].

Ranoux et al. In a study they conducted in 2012, the effects of botox and dysport on cervical dystonia were examined in 54 patients as a double-blind, randomized, crossover study. Patients were given the following treatments in a randomized order; They usually planned an effective dose of Botox, a 1:3 dose of Dysport (3 conversion factors between Botox and Dysport units), so one Botox unit = three Dysport units a 1:4 dose (four conversion factors). Each of the three scales of Tsui (primary outcome criteria) and TWSTRS pain at baseline and controls were evaluated at the follow-up visit 1 month later. When comparing Tsui scores and TWSTRS pain scores, they found that Dysport showed a better effect compared to Botox with a ratio of 1:3 ($p = 0.02$ and 0.04 , respectively) and 1:4 ($p = 0.01$ and 0.02 , respectively). They recorded the most common adverse effect as dysphagia. In conclusion, they found that Dysport 1:3 (and Dysport 1:4, largely) was more effective than Botox for both deterioration and pain in cervical dystonia, although minor side effects were observed [36].

Tilden et al. In their 2016 study, they evaluated the cost-effectiveness of incobotulinumtoxin-a with flexible treatment intervals compared to onabotulinumtoxin-a in the treatment of blepharospasm and cervical dystonia. To compare the cost and health benefits of Incobotulinumtoxin-A with those of Onabotulinumtoxin-A, they developed a Markov state transition model to perform a cost-benefit analysis. Cost-benefit analysis compared treatment with incobotulinumtoxin-A at intervals of at least 6 weeks and at intervals of no more than 20 weeks, and administration of Onabotulinumtoxin-A at intervals of at least 12 weeks and at intervals of up to 20 weeks. The Markov model consists of three health phenomena and includes the follow-up of patients in weekly cycles for 5 years. They only examined the direct health costs associated with the intake and administration of type A botulinum neurotoxins. Benefit values were derived from a prospective open-label cohort study. The cost-effectiveness of incobotulinumtoxin-A compared with onabotulinumtoxin-A in both blepharospasm and cervical dystonia was found to be US\$25,588 and US\$23,794 (cost/quality adjusted life) per year, respectively. They stated that incobotulinumtoxin-A, administered at flexible treatment intervals determined by the needs of the patient, is a cost-effective treatment option compared to the administration of onabotulinumtoxin-A in the Australian healthcare system [37].

Botulinum neurotoxin has revolutionized the treatment of spasticity and is now

applied worldwide. There are currently three leading botulinum neurotoxin type A products in the Western Hemisphere: onabotulinum toxin-A (ONA) Botox (®), abobotulinum toxin-A (ABO), Dysport (®), and incobotulinum toxin A (INCO, Xeomin (®)). There is intense debate regarding the comparability of the various preparations, although their efficacy is similar. To this end, Scaglione reviewed and compiled safety issues such as potency and conversion rates, toxin release, and immunogenicity to provide guidance for the use of BoNT-A in clinical practice. He noted that INCO was as effective as ONA with an adverse event profile when a 1:1 clinical conversion ratio was used. When he reviewed the available clinical and preclinical data, he stated that an ABO:ONA conversion ratio of 3:1 or less may be appropriate for treating spasticity, cervical dystonia, and blepharospasm or hemifacial spasm. As a result, these three products showed similar efficacy when dosed appropriately, while ABO had a better cost-effectiveness profile [38].

Studies in which a systematic pairwise comparison of all available botulinum toxin serotype A and B treatments for cervical dystonia (CD) are scarce in the literature. Han et al. In their 2016 review, five botulinum toxin products: Dysport (®) (abobotulinumtoxinA), Botox (®) (onabotulinumtoxinA), Xeomin (®) (incobotulinumtoxinA), Prosigne (®) (Chinese botulinum toxin serotype A) and Myobloim examined its effectiveness for dystonia management. Based on the clinical results reported in the literature, a two-way comparison of efficacy and safety was made for all toxins. They used the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) to evaluate efficacy. They found that all botulinum toxin serotype A and serotype B treatments were effective compared to placebo in the treatment of cervical dystonia, with the exception of Prosigne. There was no significant difference in efficacy between Dysport, Botox, Xeomin and Myobloc at the fourth week after the injection, and no significant difference was found between the treatment and placebo groups for side effects of dysphagia and injection site pain in the treatment or placebo groups [39].

Dressler et al. In their study conducted in 2014, they compared the use of OnabotulinumtoxinA (Botox (®)) and incobotulinumtoxinA (Xeomin (®)) as a botulinum toxin treatment for cervical dystonia. For this purpose, 40 cervical dystonia patients (26 female, 14 male, age at the beginning of treatment 52.6 ± 12.0 years, duration of dystonia at the beginning of treatment 10.0 ± 9.2 years, Tsui score 9.1 ± 3.9) were compared by first giving Botox (®) and then Xeomin. Botox doses were varied based on a 1:1 conversion ratio, administering 27.5 ± 13.1 treatment cycles for each patient (18.4 ± 12.4 with Botox (®) and 9.2 ± 4.5 with Xeomin (®)). They completed the treatment period as 11.3 ± 1.0 weeks (Botox (®)) 11.2 ± 1.1 weeks, Xeomin (®) 11.4 ± 1.3 weeks). As a result, they found that the efficacy of both botox drugs was similar [40].

Odergren et al. In their study in 1998, they conducted a double-blind, randomized, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. They randomized patients who predominantly had rotational cervical dystonia and who had previously received 4 sessions of Botox treatment to groups that would receive Dysport and Botox. They evalu-

ated patients two, four, eight, and 12 weeks after treatment. A total of 73 patients (Dysport, 38; Botox, 35) were treated, and they applied an average of 477 units (131) (range 240-720) to the Dysport group and 152 (45) (range 70-240) units to the Dysport and Botox groups. They found no statistically significant difference between the mean Tsui scores after treatment for the Dysport group (4.8 (0.3)) and Botox group (5.0 (0.3)) ($p = 0.66$). As a result of the global efficacy and safety evaluation, they stated that the treatment of 29 of 38 (76%) Dysport patients and 23 of 35 (66%) Botox patients was successful. ($p=0.32$) [41].

Cervical dystonia is characterized by involuntary contractions of the cervical muscles and causes abnormal posture in the head and neck [42]. Impaired motor control with simultaneous activation of both agonist and antagonist muscles is the most common form of focal dystonia [43]. Although motor problem is in the foreground, somatosensory disorders are also seen [44]. Other compelling symptoms include pain, abnormal head posture, and tremor [45]. The mental stress caused by this situation also causes dysfunction in major daily life activities such as work life and social activities [46].

In patients with cervical dystonia; rotation (torticollis); lateral tilt (laterocollis); flexion (anterocollis); extension (retrocollis); and one or more of the posture conditions such as lateral shifting can be seen [31]. Cervical dystonia can occur in various forms such as torticollis, laterocollis, anterocollis and retrocollis, in isolation or in combination [47]. An important aspect of dystonia is insufficient muscle relaxation and limitation of normal joint range of motion [45]. Insufficient muscle relaxation leads to increased activity in the agonist and antagonist muscles. This causes voluntary and sequential movements to be made more difficult [48]. Botulinum toxin is currently the preferred treatment for focal dystonia. However, studies have stated that multidisciplinary approaches, including physiotherapy, will be better in terms of treatment outcomes [49].

There are not many studies on physiotherapy yet. When we examine the literature, we see that different physiotherapy methods such as manual therapy and kinesiotherapy [50], postural reeducation exercises [51], strengthening exercises for dystonic muscles [46][52], vibration application to dystonic muscles for sensory stimulation [53], EMG biofeedback [49] are applied.

Queiroz et al. used The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and SF-36 as assessment methods in their study on 70 patients. They used motor learning exercises, kinesiotherapy and FES (Functional Electrical Stimulation) methods to antagonist muscles as physiotherapy content in their studies where they applied botox and physiotherapy together to one group and only botox to the other group. The motor learning program is designed to develop positive body image in patients, and repetitive movements are shown in the opposite direction of dystonic movements, which the patient will do by himself or in the company of a physiotherapist. When the patient reached the correct performance without assistance, more difficult exercises were started. Each session lasted an average of 20 minutes. The content of kinesiotherapy includes stretching exercises, passive and active exercises. Each session is on average 25 minutes. In FES, the ipsilateral

sternocleidomastoid, contralateral splenius and trapezius (cervical part) muscles were stimulated to torticollis; contralateral sternocleidomastoid, trapezius (cervical part), and splenius muscles are stimulated in the laterocollis. Physiotherapy with Botox has improved symptoms and improved quality of life. This study reported that the combined application of a physiotherapy program including motor learning exercises, kinesiotherapy and muscle strengthening combined with botox was effective in improving disease severity, pain and quality of life in patients with cervical dystonia [54]. All studies compared the physiotherapy program administered with Botox and the Botox treatment alone. All studies showed significantly better scores for pain and disability in groups receiving Botox treatment with an additional PT program. Physiotherapy programs applied in patients with cervical dystonia generally consist of intensive motor learning exercises (postural control, balance, strengthening of axial muscles and facilitating voluntary movement) and mobilization techniques of cervical spine and dystonic muscles. The average session duration of physiotherapy programs ranges from 40 minutes to 90 minutes [55]. Although Botox is one of the best treatment options for cervical dystonia, adding physiotherapy to the treatment will produce better results. Recent studies have revealed that patients with isolated dystonia have other non-motor features in addition to movement disorder. Sensory anomalies may precede movement disorders for months. Mild neck discomfort may precede cervical dystonia, initial eye irritation, or dry eye or throat irritation that heralds the onset of spasmodic dysphonia [56]. Pain can occur in 70% of patients with cervical dystonia [57]. Dystonia is also associated with neuropsychiatric diseases. Depressive disorders can be seen more frequently, especially in patients with cervical dystonia. Traditionally, tremor has been considered a movement disorder separate from dystonia, but recent consensus classification has confirmed that dystonic movements can occur as isolated tremor [58]. In patients with dystonia, tremor usually involves the head or arms, which may be postural/kinetic or at rest [59]. Head tremor is highly specific to dystonia, but isolated arm tremor can be confused with essential or Parkinson's tremor [60].

7. Conclusion

Among the physiotherapy approaches in dystonia; Various methods are recommended, including passive or active mobilization techniques, stretching of dystonic muscles, relaxation and electrotherapy. In approaches where different physiotherapy methods and Botox application are applied in combination, better results were found in improving disability and pain compared to Botox application alone. However, this is still a controversial issue for which no consensus has been reached, especially for patients with cervical dystonia [61].

Consent for publication

All authors read and approved the manuscript.

Competing interests

The authors declare that they have no conflict of interests.

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