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Botulinum Toxin Type A Application Experiences in Bolu Abant İzzet Baysal University Neurology Clinic

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ABSTRACT

Aim: The aim of this study was to evaluate the effects of different clinical applications of BoNT-A as hemifacial spasm, blepharospasm, cervical dystonia, bruxism, head tremor and spasticity in stroke, Multiple Sclerosis (MS), spinal trauma, hereditary spastic paraplegia, cerebral palsy, and chronic migraine.

Material and Methods: In this retrospective study, which was conducted between January 2019 and December 2021, 79 patients with movement disorders, spasticity, and chronic migraine monitored in our clinic and whose BoNT-A injections were applied were included. The diagnosis and treatment, side effects encountered in therapy, follow-up during the treatment, and the response to the treatment evaluated subjectively by patients were discussed.

Results: The improvement in patients' response to treatment was subjectively reported by themselves. The improvement in the response of the patients to the treatment subjectively stated that improvement of 60% and above was taken as good, improvement between 59-40% moderate, and improvement of 39% and below bad. Accordingly, 78.94% of the patients subjectively stated improvement as good, 13.15% as moderate, and 7.89% as bad. Although the incidence of complications was 9.21%, these side effects were mild and transient in all of the patients and did not cause any of the patients to discontinue the treatment.

Conclusion: The results were statistically significant and consistent with the literature. This study supports the fact that botulinum toxin therapy is effective and safe for HS, BS, cervical dystonia, spasticity, bruxism, head tremor, and chronic migraine.

Keywords: Botulinum toxin; blepharospasm; dystonia; hemifacial spasm; spasticity.

Bolu Abant İzzet Baysal Üniversitesi Nöroloji Kliniğinde Botulinum Toksin Uygulamaları Deneyimleri

ÖZ

Amaç: Bu çalışmanın amacı, nöroloji klinik uygulamalarında uzun zamandır önemli yer tutan Botulinum Nörotoksin tip A(BoNT-A)'nın hemifasiyal spazm(HS), blefarospazm(BS), servikal distoni, bruksizm, baş tremoru gibi hareket hastalıklarıyla; inme, multiple skleroz(MS), spinal travma, herediter spastik parapleji(HSP) ve serebral palsi gibi farklı spastisite çeşitlerinde ve kronik migrende, uygulamalarının klinikteki etkilerini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Ocak 2019 – Aralık 2021 tarihleri arasında kliniğimizde izlenen, aynı nörolog tarafından BoNT-A tedavileri uygulanan ve takip edilen;HS, BS, spastisite, servikal distoni, bruksizm,baş tremoru ve oral medikal tedaviye dirençli kronik migrenli, yaşları 21-85 arası 79 hastanın tanı ve tedavisi, tedavi doz ve uygulama şekilleri ile BoNT-A'ya verilen yanıtlar, tedavide sık görülen yan etkiler, tedavi süresince yapılan hasta takipleri ve hastalar tarafından subjektif olarak değerlendirilen tedaviye yanıtları, betimleyici istatistikler kullanılarak raporlanmış ve literatür eşliğinde tartışılmıştır.

Bulgular: Hastaların, tedaviye yanıtlarındaki düzelme ilaç enjeksiyonundan yaklaşık bir ay sonra kontrol muayeneye geldiklerinde belirttikleri şekilde değerlendirildi. Hastalar, subjektif olarak %60 ve üzeri düzelmeyi iyi, %59-40 arası düzelmeyi orta, %39 ve altı düzelmeyi kötü olarak ifade etti. Buna göre hastaların %78,94'ü subjektif olarak iyileşmeyi iyi, % 13,15'i orta ve % 7,89 i kötü olarak belirtti. Komplikasyon insidansı % 9,21 olmasına rağmen bu yan etkiler tüm hastalarda hafif ve geçici olup hiçbir hastanın tedaviyi bırakmasına neden olmadı.

Sonuç: Sonuçlar literatürle uyumlu olarak anlamlıydı. Bu çalışma, BoNT-A tedavisinin HS, BS, Servikal distoni, inme sonrası spastisite, serebral palsi, bruksizm, baş tremoru ve kronik migren için etkili ve güvenli bir tedavi olduğu gerçeğini desteklemektedir.

Anahtar Kelimeler: Botulinum toksini; blefarospazm; distoni; hemifasiyal spazm; spastisite.

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INTRODUCTION

BoNT-A is one of seven toxins produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium. When BoNT-A is injected into the muscle, it is taken up by endocytosis from the presynaptic nerve-end at the neuromuscular junction, which inhibits acetylcholine release by affecting fusion proteins. Botulinum neurotoxin causes flaccid paralysis by blocking acetylcholine secretion at the neuromuscular junction and this chemical denervation stops spasticity and involuntary movements in the muscle. Post-injection muscle relaxation starts on the 5th-7th days and usually lasts for 12-16 weeks. This may be followed by longitudinal muscle growth and the effect may last up to 6 months (1-5).

Treatment applications of BoNT-A in clinical medicine have increased in the last 25 years in movement disorders (dystonia, tremor), cerebral palsy, autonomic dysfunction such as excessive sweating and neurogenic bladder, spasticities such as MS, spinal trauma, HSP, and HS, blepharospasm BS, and hyperactive muscle diseases of the facial area. In recent years, it has been used frequently in the treatment of essential head and hand tremors, Parkinson's tremors, and chronic migraine (4-8).

The aim of this retrospective study is to evaluate the efficacy and side effects of Botulinum Neurotoxin type A (BoNT-A), which has long been an important treatment in neurology clinical practice in motion sicknesses such as hemifacial spasm (HS), blepharospasm (BS), cervical dystonia, bruxism, head tremor; in different types of spasticity such as stroke, multiple sclerosis (MS), spinal trauma, hereditary spastic paraplegia (HSP), cerebral palsy, and pain treatments such as chronic migraine resistant to medical treatment.

MATERIAL AND METHODS

The Ethics Committee of Bolu Abant İzzet Baysal University (2021-313) approval was received for the study. The article complied with the Research and Publication Ethics. Informed Consent was obtained from all patients. Patients who were not followed up regularly in our clinic and who were followed up in different clinics and centers were excluded from the study. Repeated visits of the patients were not counted, the first visit of each patient was taken as a basis, and the patients who applied for regular controls were included in the study. All of them were examined and treated by the same neurologist.

During the current follow-up years, approximately 175 applications were made to the patients. The number of injections during each toxin administration varied according to the patients and their clinical diagnoses. Before the BoNT-A application, attention was paid to its compliance with the cold chain conditions (2-8°C). To ensure homogeneity, only the patients who received BoNT-A (Botox®) were included in the study, other patients were not included. BoNT-A injections can be made into different parts of the orbicularis oculi (OO) muscle (orbital, preseptal, and pretarsal). The initial dose (1.25-2.4 U) was preferred for Botox, and the dose was increased in maintenance therapy. Electromyography (EMG) guidance was not required during these applications. For HS and BS, the pretarsal part of the OO muscle was mostly treated as BoNT-A application. Injections were made into the lateral and medial OO muscles of the upper eyelid. For BS, injections were made into the lateral OO, frontalis, nasalis, and zygomaticus. In subsequent applications, the dose to be administered was adjusted according to the patient's response to treatment. In patients treated for bruxism, injections were made in the area below the ear-mouth line at three points in the maxillary and two points in the temporal regions (9-12).

Generally accepted dosages for muscle groups: For BoNT-A, 3-6 U/kg per muscle in the lower extremity, 2-3 U/kg per muscle above the elbow in the upper extremity, 0.5-2 U/kg per muscle in the upper extremity below the elbow, tibialis posterior, flexor hallucis longus, and other small muscles is applied. The small muscles of the palm (adductor pollicis, opponents pollicis, and lumbricals) are exceptionally applied at a lower dose than this dose. For example, if the thumb participates in the grip function, 5-7.5 U is applied in total. Generally, 12 U/kg/session and a maximum of 300U should be applied in one session. Injection frequency should not be less than 3 months. Generally, the injection should be administered every 6 to 12 months. The maximum dose administered to each injection site should not exceed 50 U. Generally, two or three injection sites are used for large muscles (gastrosoleus or medial hamstring), two injection sites for medium-sized muscles (hip adductors, biceps brachii), and one injection site for smaller muscles (flexor carpi radialis, adductor pollicis)(13,14). They are diluted with isotonic saline solution and administered intramuscularly. Injections at short intervals (less than 3 months) and high doses (more than 300 MU Botox® or 1500 MU Dysport®) can lead to the development of antibodies and loss of efficacy and should therefore be avoided (6-8, 15, 16).

Use of BoNT-A in Spasticity: Spasticity means an increase in tone in one of the flexors or extensor muscle groups, resulting in posture disorder, pain, and decreased mobility. One of the treatment methods of BoNT-A injection is a well-tolerated, safe, and effective procedure in the treatment of focal spasticity. Contracture and other lesions that may occur as a result of involuntary contraction can be prevented. BoNT-A applications in spasticity are mostly applied in cases of post-stroke, cerebral palsy, secondary to trauma, MS, and HSP (14, 17).

Use of BoNT-A in Dystonia: Dystonia means simultaneous contraction of flexor and extensor-agonist and antagonist's muscles. It is frequently used in the dystonias of patients with torticollis and cerebral palsy, especially in cervical dystonia. Cervical dystonia is a focal dystonia that affects muscles of the neck and shoulder, and it causes characteristically recurrent tonic and clonic movements leading to abnormal head and neck postures (18-20).

Use of BoNT-A in HS-BS:

BS, which occurs with an involuntary contraction of the muscles around the eyes, and HS, which causes involuntary contraction of unilateral facial muscles and the muscles around the nasolabial sulcus, are two important facial dyskinesias. Although the etiology of BS is not known exactly, it is thought to occur as a result of overstimulation of brainstem neurons due to degenerative changes in the basal ganglia. HS, on the other hand, usually occurs due to vascular compression occurring at the root of the facial nerve. In two disease groups, The first treatment option is BoNT-A injection.

Although BoNT-A injection is a very effective and safe treatment method for both diseases, it is necessary to repeat the treatment after a while. While many studies have shown that repeated BoNT-A injections don't cause a change in the duration of well-being, some studies have shown that it causes a prolongation of the duration of well-being (21-23).

Statistical Analysis

In this study, the records of 79 patients who were followed up in our clinic and received BoNT-A injections were reviewed retrospectively. The patients' diagnoses, treatment schemes, responses to BoNT treatment, side effects encountered during the treatment, follow-up of the patients during their treatment, and subjective evaluations of the response to the treatment of the patients were reported and discussed. Descriptive statistics were given as the number of units (n) and percent (%) values (Table 1).

RESULTS

In this study, in which 48 female and 30 male (n=78) patients with movement disorders, spasticity, and chronic migraine who received BoNT-A injection in our clinic between January 2019 and December 2021 were evaluated retrospectively. The diagnosis and treatment, responses to BoNT-A, side effects, and subjectively evaluated responses to treatment by patients were reported and discussed in this respect.

A total of 79 patients, (48 women, average age: 62.59) and (31 men, average age: 60.44), were followed up and treated. The ages of the patients ranged from 23 to 85 (mean: 61.40). A total of 25 (31.65%) [(17 women, 8 men)] patients with HS, 15 (18.99%) [(8 men, 7 women)] patients with BS, 8 (10.13%) [(6 women, 2 men)] patients with cervical dystonia (in the form of spasmodic torticollis), 11 (13.92%) [(5 men, 6 women)] patient with spasticity after stroke, 3 (3.80%) [(2 women, 1 man)] patients with spasticity associated with cerebral palsy, 2 (2.53%) [(1 woman, 1 man)] patients with spasticity associated with spinal trauma, 2 (2.53%) [(men)] patients with MS related spasticity, 1 (1.23%) [(man, 54 years)] patient with HSP, 4 (5.06%) [(2 men, 2 women)] patients with bruxism, 2 (2.53%) patients with head tremor [(1 woman, 1 man)] and 6 (7.59) patients with chronic migraine who were resistant to oral medical therapy were followed up (Table 1).

The subjective improvements in the response of the patients to the treatment were reported as 60% and above as good, improvement between 59-40% as moderate, and improvement of 39% and below as bad. Accordingly, 78.94% of the patients subjectively stated improvement as good, 13.15% as moderate, and 7.89% as bad. Although the incidence of complications was 9.21%, these side effects were mild and transient in all of the patients and did not cause any of the patients to discontinue the treatment (Table 1).

In 6 female patients who received chronic oral medical treatment for migraine for a long time and could not benefit, 100 IU BoNT-A treatment was applied to the right and left corrugator, frontalis, temporal, occipital, trapezius, cervical, and upper occipital regions (10). In the first BoNT-A application, 3 (3.80%) patients had good treatment response, 2 (2.53%) had moderate, and 1 (1.27%) had poor treatment response (Table 1).

One minute after the injection, an elderly female patient (73 years old, HS) had syncope while on a stretcher, who said that she had not taken her antihypertensive medication that day, and a young patient (38 years old male, spasticity) after a stroke had a hypotensive shock and recovered. Both patients had syncope for about 1-2 minutes and recovered. Arterial blood pressure, blood glucose levels, and oxygen saturations were measured as normal. It was their first injection for both patient.

Administration of BoNT-A required additional dose injection in the following two situations: To correct asymmetry in the non-injected half of the face in the HS patient and for partially sustained contractions in one cervical dystonia patient.

All of the patients included in the study had not been previously treated with BoNT-A. Before toxin administration, three patients used biperiden, two patients used carbamazepine, three patients used gabapentin, and six patients used baclofen and did not benefit. It was observed that these treatments were discontinued a few days before the patients who received medical treatment before switching to injection treatment. During the follow-up period of the patients, no side effects developed at a level that made them discontinue the application. Dry eye, stinging pain in the eyes, and pain and ecchymosis at the injection site developed in five cases. Ptosis developed in three HS patients during follow-up, and these side effects resolved in 4–6 weeks. Syncope developed in two patients, one hypertensive and the other hypotensive, lasting approximately 1 minute. Although the incidence of complications was 12.9%, these side effects were mild and transient in all of the patients and did not cause any of the patients to discontinue the treatment (12, 24-26).

HS usually begins between the ages of 40 and 50 and is more common in women than men. HS is a more common disease than BS (11, 12). In our study, HS was detected in women in their 40s. Consistent with the literature, HS cases were observed more frequently than BS in our study (Table 1).

BoNT-A treatment in spasticity: While there is a significant benefit especially in post-stroke patients (good), secondarily cerebral palsy (good), it was beneficial at least in hereditary spastic paraplegia (bad), secondarily, in spasticity secondary to spinal trauma (bad), and then in patients with multiple sclerosis (moderate) (14, 17, 20).

In 1 of the Chronic Migraine Patients, the benefit from BoNT-A treatment is feedback in the form of almost 100% recovery with 2 patients, good, 2 patients moderate, and 1 patient bad (12, 24-27). With the treatment applied to 2 patients with essential head tremors (1 female, 1 male) in total, the feedback of the patients was close to 100% improvement in their complaints.

Table 1. Demographic characteristics of the patients

	Female		**Male**		**Response of Treatment**						**Side effects**					
Diseases					**Good ≥60%**		**Moderate 59-40%**		**Bad ≤39%**		**Eye burning and redness**		**Ptosis**		**Syncope**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hemifacial Spasm	17	21.52	8	10.13	25	31.7	0	0	0	0	2	2.53	3	3.80	1	1.27
Blepharospasm	7	8.86	8	10.13	15	19.0	0	0	0	0	1	1.27	0	0	0	0
Spasticity (Poststroke)	6	7.59	5	6.33	7	8.86	2	2.53	2	2.53	0	0	0	0	1	1.27
Spasticity (Cerebral Palcy)	2	2.53	1	1.27	2	2.53	1	1.27	0	0	0	0	0	0	0	0
Spasticity (Multiple Sclerosis)	0	0	2	2.53	0	0	1	1.27	1	1.27	0	0	0	0	0	0
Spasticity (Spinal Trauma)	1	1.27	1	1.27	0	0	1	1.27	1	1.27	0	0	0	0	0	0
Spasticity (Hereditary Spastic Paraplegia)	0	0	1	1.27	0	0	0	0	1	1.27	0	0	0	0	0	0
Cervical Dystonia	6	7.59	2	2.53	6	7.59	2	2.53	0	0	0	0	0	0	0	0
Chronic Migraine	6	7.59	0	0	3	3.80	2	2.53	1	1.27	0	0	0	0	0	0
Bruxism	2	2.53	2	2.53	2	2.53	1	1.27	1	1.27	0	0	0	0	0	0
Head Tremor	1	1.27	1	1.27	2	2.53	0	0	0	0	0	0	0	0	0	0
Total	48	60.76	31	39.24	62	78.5	10	12.7	7	8.86	3	3.80	3	3.80	2	2.54

DISCUSSION

Although various drugs (trihexyphenidyl, diazepam, clonazepam, biperiden, bornaprine, tetrabenazine, carbamazepine, levodopa) have been used especially in movement disorders such as HS and BS, BoNT-A is accepted as the gold standard (21).

It is pointed out that, BoNT-A is an effective treatment for patients with post-stroke spasticity, with more than half of patients responding to treatment, even after a single injection. Treatment success and duration are inversely proportional, and the benefit of injections made after the first 36 months after stroke was less than before (11,12,21,22). More than 60% benefit was achieved with BoNT-A treatment applied to the upper extremity proximal and medium-sized muscles of our patients; on the other hand, less than 40% response was obtained after the treatment of the wrist and hand muscles. It was observed that the patients who were treated for lower extremity proximal and distal muscles improved more than 60% in the post-treatment evaluations. Response to treatment was less than 40% in two male patients aged 62 and 54 years who had a bilateral stroke and were treated for spasticity.

In the literature, it has been reported that local side effects such as pain, edema, ecchymosis, and hyperesthesia at the injection site occur in BoNT-A injections and that these toxin-related side effects are generally well tolerated (9-11). Similarly, it was found that these side effects occurred at the same rate in patients treated in our clinic, and it was observed that these patients generally tolerated the side effects of toxins well (Table 1).

In addition, it has been shown that applications to the pretarsal part of the orbicularis oculi muscle give more successful results than applications to the pretectal region and cause a decrease in the frequency of ptosis, which is the most important side effect (12,24,25,28). In our study,

in accordance with the literature, ptosis was observed in only three patients (3.80%) in BoNT-A applications to the pretarsal part of the orbicularis oculi muscle (Table 1).

For cervical dystonias, many studies have shown that BoNT-A injection is beneficial and its efficacy is a reliable treatment method (24-26). In our patients, no side effects were observed in any cervical dystonia patient. In one patient, the efficacy of the treatment ended after two months, but it was waited for three months to apply the treatment again so that resistance (antibody) did not develop. Besides, none of the patients had adverse effects. Findings obtained from patients with cervical dystonia who were treated are consistent with the findings of many researchers (Table 1).

Sorgun et al. (29) compared the results of many studies with different scales that they systematically reviewed and documented with their study on patients with HS. They showed that an improvement between 70% and 98% was achieved according to the data obtained. In our clinic, as a result of the BoNT-A application applied to 25 patients with HS, it was observed that all patients recovered well (Table 1).

Studies conducted on patients with BS have shown that 90% improvement is achieved (30-32). In our clinic, as a result of the BoNT-A application, which was applied to 15 patients with BS, it was observed that a good level of improvement was achieved in all of the patients (Table 1). In some elderly patients with BS, HS, and cervical dystonia, a reduced dose was applied to avoid side effects due to the reduction of muscle, fat and connective tissue.

In this study, when all the patients were evaluated by the literature, in the indications of BoNT-A application mentioned so far, positive results have been obtained with clinical follow-up and patient feedback. To avoid efficacy and side effects, for the patient, considering the skin, subcutaneous connective tissue, and muscle tissue of each patient, the complication rate can be greatly reduced by paying more attention to the doses in patients with atrophy and sarcopenia (11,12,24,25).

The limitations of the study were that it had a retrospective and single-center design. Prospective and multicenter studies with more patients may contribute more to the clarification of the subject.

CONCLUSION

These results were found to be similar to those in the literature. This study supports the fact that local botulinum toxin therapy is an effective, safe, and long-lasting preventive treatment for HS, BS, Cervical dystonia, post-stroke spasticity, cerebral palsy, head tremor, bruxism, and chronic migraine.

Unlike the literature, chronic migraine and bruxism patients reported more than fifty percent well-being. Unlike the literature, the placebo effect and close attention are thought to be factors that increased the success of treatment in these patients (27, 33).

More multicenter, widespread clinical studies are needed, especially to have more information about new treatment applications.

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REFERENCES

1. Simpson LL. The origin, structure, and pharmacological activity of botulinum toxin. Pharmacol Rev. 1981; 33: 155-88.

2. Jankovic J, Albanese A, Atassi MZ, Dolly JO, Hallet M, Mayer N. Botulinum toxin E-Book: Therapeutic clinical practice and science. Elsevier Health Sciences. 2008.

3. Akdemir MO, Uğurbaş SC, Uğurbaş SH. Benign esansiyel blefarospazm ve hemifasiyal spazm tedavisinde botulinum toksin uygulamasının uzun dönem etkisi. Turk J Ophthalmol. 2015; 45(1): 9-13.

4. Evidente VGH, Adler CH. Hemifacial spasm and other craniofacial movement disorders. Mayo Clin Proc. 1998; 73(1): 67-71.

5. Ramirez-Castaneda J, Jankovic J. Long-term efficacy and safety of botulinum toxin injections in dystonia. Toxins. 2013; 5(2): 249-66.

6. Mittal S, Machado D. Botulinum toxin in parkinson disease tremor: A randomized, double-blind, placebo-controlled study with a customized ınjection approach. Mayo Clin Proc. 2017; 92(9): 1359-67.

7. Siddiqui M, Shah PV, Balani P, Lopez A R, Nobleza CMN, Khan S. Comparing the efficacy, safety, and superiority of calcitonin gene-related peptide monoclonal antibodies and botox in preventing and treating migraines. Cureus, 2021; 13(1): e13002.

8. Burç H, Atay T, Baykal YB, Baydar M L, Kırdemir V. Serebral palside botulinum toksininin yeri. Medical Journal of Suleyman Demirel University. 2011; 18(2): 78-81.

9. Trosch RM. Pullman SL. Botilinum toxin A injections for the treatment of hand tremors. Movement disorders: official journal of the Movement Disorder Society. 1994; 9(6): 601-9.

10. Shuhendler AJ, Lee S, Siu MM, Ondovcik M S, Lam MK, Alabdullatif MA et al. Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2009; 29(7): 784-91.

11. Altun Y. Botulinum toxin application experiences in Adıyaman University, Department of Neurology: A retrospective study. Kafkas J Med Sci. 2017; 7(2): 134-8.

12. Cakmur R. Blefarospazm ve hemifasiyal spazmda botulinum toksini tedavisi/botulinum toxin treatment of blepharospasm and hemifacial spasm. Noro-Psikyatri Arsivi. 2010; 47: 6-10.

13. Green P, Fahn S, Diamond B. Development of resistance to botulinum toxin type A in patients with torticollis. Mov Disord. 1994; 9(2): 213-7.

14. Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. Neurology. 1995; 45(4): 712-7.

15. Ünlü E, Cevikol A, Bal B, Gonen E, Celik O, Kose G. Multilevel botulinum toxin type A as a treatment for spasticity in children with cerebral palsy: A retrospective study. Clinics. 2010; 65(6): 613-9.

16. Karaca B, Ünlü E, Köse G, Gönen E. Çakcı A. Outcomes of botulinum toxin type A injection followed by rehabilitation in cases of cerebral palsy with upper

extremity involvement. Journal of Child. Neurology. 2016; 31(3): 357-63.
17. Simpson DM. Clinical trials of botulinum toxin in the treatment of spasticity. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 1997; 20(S6): 169-75.
18. Karp BI. Treatment of limb dystonia with Botilinum Toxin. American Academy of Neurology. 2001; Syllabi-on-CD-Rom, Clinical Usefulness of Botilinum Toxin and Treatment of Dystonia. 2SW.001.
19. Comella CL, Brin M, Jankovic J. Botulinum toxin in the clinical management of cervical dystonia. Neurology. 2000; 55(S5): 1-35.
20. Hsiung GY, Das SK, Ranawaya R, Lafontaine AL, Suchowersky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Movement disorders: official journal of the Movement Disorder Society. 2002; 17(6): 1288-93.
21. Snir M, Weinberger D, Bourla D, Kristal-Shalit O, Dotan G, Axer-Siegel R. Quantitative changes in botulinum toxin a treatment over time in patients with essential blepharospasm and idiopathic hemifacial spasm. American journal of ophthalmology. 2003; 136(1): 99-105.
22. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. Clinical & experimental ophthalmology. 2014; 42(3): 254-61.
23. Jankovic J. Schwartz K. Botulinum toxin treatment of tremors. Neurology. 1991; 41(8): 1185-1185.
24. Anderson TJ, Rivest J, Stell R, Steiger MJ, Cohen H, Thompson PD, et al. Botulinum toxin treatment of spasmodic torticollis. Journal of the royal society of medicine. 1992; 85(9): 524-9
25.Tüfekçi A. Botulinum toksini uygulamalarında olası yan etkiler ve takipleri. Turkiye Klinikleri J Neurol-Special Topics. 2013; 6(4): 46-51.
26. Matur Z, Parman YG. Spastisite tedavisinde a tipi botulinum toksini kullanimi/Use of botulinum toxin type a in the treatment of spasticity. Noro-Psikyatri Arsivi. 2010; 47: 40-3.
27. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. Journal of neural transmission. 2013; 120(2): 275-90.
28. Nüßgens Z, Roggenkämper P. Comparison of two botulinum-toxin preparations in the treatment of essential blepharospasm. Graefe's archive for clinical and experimental ophthalmology. 1997; 235(4): 197-9.
29. Sorgun MH, Yilmaz R, Akin YA, Mercan FN, Akbostanci MC. Botulinum toxin injections for the treatment of hemifacial spasm over 16 years. Journal of Clinical Neuroscience. 2015; 22(8): 1319-25.
30. Costa J, Espírito-Santo CC, Borges AA, Ferreira J, Coelho MM, Moore P, et al. Botulinum toxin type A therapy for blepharospasm. Cochrane Database of Systematic Reviews. 2004; 2.
31. Duarte GS, Rodrigues FB, Marques RE, Castelao M, Ferreira J, Sampaio C, et al. Botulinum toxin type A therapy for blepharospasm. Cochrane Database of Systematic Reviews. 2020; 11.
32. Bhidayasiri R, Cardoso F, Truong DD. Botulinum toxin in blepharospasm and oromandibular dystonia: comparing different botulinum toxin preparations. European Journal of Neurology. 2006; 13: 21-9.
33. Anandan C, Jankovic J. Botulinum toxin in movement disorders: An update. Toxins. 2021; 13(1): 42.