Tear meniscus, corneal topographic and aberrometric changes after botulinum toxin-a injection in patients with blepharospasm and hemifacial spasm

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Abstract

Purpose To investigate the effect of botulinum neurotoxin-A (BTX-A) treatment on dry eye symptoms, tear meniscus, corneal topography and corneal aberrometry in patients with benign essential blepharospasm (BEB) and hemifacial spasm (HFS).

Materials and methods This prospective study comprised of 6 patients with BEB and 20 patients with HFS. Tear meniscus height (TMH) and depth (TMD), tear break-up time (TBUT), corneal fluorescein staining score (CFSS), Schirmer I test, ocular surface disease index (OSDI) score, corneal topography [corneal power of flat axis (K1), corneal power of steep axis (K2), mean corneal power (Km), astigmatism and thinnest pachymetry] and anterior corneal aberrometry [spherical aberration (SA), vertical coma (vcoma), horizontal coma (hcoma), higher order root mean square (hRMS) and total RMS] were evaluated before BTX-A treatment, 3 weeks after BTX-A treatment and 2 months after BTX-A treatment.

Results Six patients with BEB and 20 patients with HFS treated with BTX-A were evaluated in this study. Twenty contralateral spasm free eyes of 20 HFS patients were taken as control group. TMH and TMD were found to be significantly higher in eyes with spasm at both 3 weeks and 2 months after injection (TMH: 279.0 ± 123.2 at pretreatment, 380.5 ± 174.7 at third week and 317.0 ± 125.5 at second month p < 0.001 and p = 0.02, respectively). (TMD: 183.7 ± 59.7 at pretreatment, 235.7 ± 91.1 at third week and 209.8 ± 77.1 at second month p < 0.01 and p = 0.015, respectively). TBUT, CFSS, Schirmer I test values were similar (p > 0.05). OSDI scores decreased significantly from 29.6 ± 25.3 to 19.8 ± 20. p = 0.03 at third week and increased again by second month. K2 (43.9 ± 1.7 vs. 43.7 ± 1.6, p = 0.03) and astigmatism (0.8 ± 0.5 vs. 0.6 ± 0.4, p = 0.04) values were significantly lower at third week and increased again by second month. Pachymetry and aberrometric values did not change significantly. In the control group only Schirmer I test value decreased significantly at second month (10.5 ± 6.5 vs. 7.2 ± 5.6, p = 0.008), other parameters did not change.

Conclusion BTX-A injection increases tear meniscus and decrease symptoms related to dry eye disease in BEB and HFS patients. It decrease astigmatism and keratometry values, it does not cause a significant change in corneal aberrations. However the positive effects of BTX-A injection on ocular surface is temporary.
Keywords  Blepharospasm · Botulinum neurotoxin-A · Corneal topography · Hemifacial spasm · Tear meniscus

Introduction

Benign essential blepharospasm (BEB) and hemifacial spasm (HFS) are two facial movement disorders characterized by involuntary and frequent contraction of the orbicularis oculi muscle which causes functional disability [1, 2]. Botulinum neurotoxin-A (BTX-A) injection is the gold standard treatment of these two diseases. It has an anticholinergic effect at the neuromuscular junction by inhibiting acetylcholine release and signal transduction. As the effect is temporary and lasts 3–6 months, repeated injections are required [3].

The frequent and strong closure of eyelids in BEB and HFS can affect tear production, tear distribution, tear drainage and cause dry eye disease (DED) [4, 5]. The effect of BTX-A on DED is controversial. Also, BTX-A treatment was reported as a cause of DED in the Tear Film and Ocular Surface Society’s Dry Eye Workshop (TFOS DEWS) II Report [6]. Ho et al. discerned a significant decrease in TBUT and Schirmer test results after BTX-A injections. When the injection side is in the lateral part of the orbicularis oculi muscle, BTX-A diffuses through the orbital septa to the lacrimal gland and decreases tear production via an anticholinergic effect on the lacrimal gland [7]. Also lagophthalmos, incomplete blinking and ectropion are other causes of dry eye associated with BTX-A treatment [8]. However, Gunes et al. have shown that BTX-A treatment significantly improved TBUT, OSDI score and CFSS in facial dystonias [9]. The tear film and ocular surface are affected in DED; as tear film thickness changes with each blink, tear meniscus measurement is used to show total tear volume [10]. The anterior segment optical coherence tomography (AS-OCT) provides high resolution images of the cornea and anterior segment and can be used for the noninvasive measurement of tear meniscus [11]. Lower tear meniscus measurements correlate well with symptoms and signs of DED [12, 13]. There are only a few studies evaluating the effect of BTX-A on the tear meniscus using AS-OCT [4, 14].

Involuntary eyelid spasms cause abnormal pressure on the corneal surface, leading to changes in corneal topography, especially in astigmatism [9, 15]. DED itself increases irregular astigmatism and higher order aberrations (HOA) [16]. Yakibu and Yoshihiko et al. reported ocular wave front changes after BTX-A treatment in patients with BEB and HFS [17, 18]. Also it is reported that corneal HOA was correlated with subjective symptoms in patients with dry eye disease [19]. However, to date, there have been no studies evaluating corneal aberrometric changes after BTX-A injections in patients with BEB and HFS. The aim of this study was to investigate the effect of BTX-A injections on dry eye signs and symptoms and corneal topographic and aberrometric parameters in patients with BEB and HFS as measured before the treatment, 3 weeks and 2 months after the treatment.

Materials and methods

Six patients with BEB (4 female, 2 male) and twenty patients with HFS (9 female, 11 male) involving the eyelids were included in this prospective study. 26 eyes of 26 BEB and HFS patients with spasm that receive Botox injection (Group 1) and 20 contralateral eyes of HFS patients without spasm and no prior botox injection history (Group 2) were evaluated. Subjects who had a history of ocular trauma, previous ocular surgery or an ocular surface disease other than dry eye, contact lens wear or topical drop use, a refractive error greater than ± 4 D or a history of neurological disorder other than dystonia were excluded from the study. The study protocol was approved by the local ethics committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants prior to enrollment.

BTX-A (Botox®) was diluted with 2 ml of 0.9% sodium chloride in order to obtain 5 U/0.1 ml injection. The toxin was injected subcutaneously with a 27-gauge insulin syringe. The total injected dose was 50–70 units for each patient. The periorbicular injection sites for patients with hemifacial spasm were as follows: Orbicularis oculi muscle (median and lateral pretarsal sections, lateral canthal region, lateral part of lower eyelid) and corrugator. The injection sites for patients with blepharospasm were orbicularis oculi muscles (median and lateral pretarsal sections, lateral canthal region, lateral part of lower eyelid) and corrugator. The injection sites for patients with blepharospasm were orbicularis oculi muscles (median and lateral pretarsal sections, lateral canthal region, lateral part of lower eyelid), corrugators and frontalis muscles bilaterally.
Patients were evaluated in terms of tear function and corneal topographic parameters before treatment, 3 weeks after the injection, and 2 months after the injection. Tear function was evaluated with measurements of lower tear meniscus height (TMH), tear meniscus depth (TMD), tear break-up time (TBUT), corneal fluorescein staining score (CFSS) (National Eye Institute grading scale) and Schirmer I test with anesthesia. TMH and TMD were evaluated by AS-OCT. AS-OCT examinations were performed using Swept Source OCT (DRI OCT Triton, Topcon, Tokyo, Japan) by the same experienced technician (NY). AS-OCT single vertical scan mode was used to measure the lower tear meniscus. The images were taken from the intersection of the line descending from the corneal vertex and the lower eyelid (Fig. 1). During the imaging procedure patients were asked to look at a fixed target within the device and blink normally. After examinations were performed, a built-in caliper was used to measure the lower TMH (between the distance from the cornea-meniscus junction to the lower eyelid-meniscus junction) and TMD (the line from the TMH to inferior fornix) in micrometers. All measurements were taken by the examiner who was blinded from other test results (NBB).

Corneal topography measurement was taken by Pentacam (Oculus, Wetzlar, Germany) in the automatic release mode by the same experienced examiner (NÖ). The corneal power of flat axis (K1), corneal power of steep axis (K2), mean corneal power (Km), corneal astigmatism, thinnest corneal thickness and anterior corneal aberrations [spherical aberration (SA), vertical coma (vcoma), higher order root mean square (hRMS) and total RMS] were evaluated.

Schirmer test was performed with topical anesthesia. 3 min after instillation of 1 drop proparacaine 0.5%, Schirmer test strip was placed to the lower a third of lateral bulbar conjunctiva. After 5 min, the length of the wetted strip was recorded as Schirmer test score.

Corneal fluorescein staining was evaluated under cobalt blue illumination. Sterile saline solution was added to a fluorescein sodium strip and then fluorescein was instilled to the inferior eyelid cul de sac. Participant was instructed to blink; after 2 min the degree of staining was graded according to the National Eye Institute grading scale [20].

In order to measure TBUT, the participant was asked to look straight-ahead and blink three times. The precorneal tear film was examined under cobalt blue illumination, the time between the final blink and appearance of the first break in the fluorescein was recorded in seconds. TBUT was measured three times and average of measurements were recorded. Schirmer test, CFSS and TBUT were conducted by the same experienced ophthalmologist (NBB).

The subjective discomfort related to dry eye was also assessed with the Turkish version of the Ocular Surface Disease Index (OSDI, Allergan Inc) questionnaire.

The statistical software package SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA) for windows was used for data analysis. Data distribution for normality was assessed using Shapiro–Wilk test. Paired t-test or Wilcoxon test were used to determine the differences between the measurements before and after BTX-A injections. Data were presented as

Fig. 1 Lower tear meniscus was measured by optical coherence tomography (OCT): a The images were taken from the intersection of the line descending from the corneal vertex and the lower eyelid, b Sagittal view of tear meniscus before botulinum neurotoxin-A (BTX-A) injection, c Sagittal view of tear meniscus after BTX-A injection
mean ± standard deviations. A p value of < 0.05 was considered statistically significant.

Results

Twenty six eyes with spasm (Group 1) and 20 contralateral eyes of HFS patients without spasm (Group 2) were enrolled in this study. The mean age of the patients in group 1 was 59.4 ± 8.8 years (39–71 years) and in group 2 was 59.10 ± 8.3 years (44–71) (p = 0.912) The mean disease duration was 5.2 ± 3.7 years (2–15 years). The mean BTX-A injection duration the patients had before was 4.4 ± 2.7 years (1–10 years) and the average time between the last and current BTX-A injection was 3.8 ± 0.8 months (3–6 months). The 26 study patients had a total of 394 BTX-A treatment visits (mean number of visits/patient 15.53 ± 11.1; range 4–40 visits/patient).

The comparison of tear and ocular surface parameters in eyes with spasm at baseline, 3 weeks and 2 months after injection are given in detail in Table 1. TMH and TMD were significantly higher at both third week (p < 0.001 for TMH and TMD) and second month (p = 0.02 for TMH and p = 0.015 for TMD) compared to baseline. At second month tear meniscus parameters showed a tendency toward decreasing. TBUT, CFSS, Schirmer I test values were similar 3 weeks and 2 months after injection (p > 0.05). OSDI scores decreased significantly at third week (p = 0.04). However, by the second month, OSDI scores increased again slightly.

Table 2 lists the topographical measurements in eyes with spasm. K2 and astigmatism values were significantly lower at third week (p = 0.03 and 0.04, respectively). By the second month, K2 and astigmatism increased again to nearly the same pre-treatment values. Pachymetry and aberrometric values did not show statistically significant differences (p > 0.05).

In the control group only Schirmer I test value decreased significantly at second month (10.5 ± 6.5 vs. 7.2 ± 5.6, p = 0.008), other parameters did not change (Tables 3, 4).

Discussion

BTX-A has been used to treat HFS and BEB since the 1980s [21]. It is a safe and effective treatment that relieves the symptoms of BEB and HFS in 66–100% of cases [22, 23].

The results of studies showing the relationship between dry eye and BTX-A treatment are contradictory. Although evaluation times are different, at the time when the effect of BTX-A is maximum, the TBUT and Schirmer test results are different between studies. While Park et al. reported an increase in TBUT and Schirmer test [4], Kocabeyoglu et al. reported an increase in TBUT and no change in Schirmer test [24]. In the other two studies, an increase in TBUT and decrease in Schirmer test was reported [9, 25]. The most likely cause of these different results is the differences in injection sites and dosages.

BTX-A injection into the lacrimal gland reduces aqueous tear secretion so it is used in the treatment of epiphora. Conversely, BTX-A injection to the lower medial canthal region is used in dry eye treatment. It decreases the blinking rate, reduces the action of

Table 1 Changes in the tear and ocular surface parameters after BTX-A injection in patients with blepharospasm and hemifacial spasm

| Variables (mean ± SD) | Before | After 3 weeks | After 2 months | p Values pretreatment vs. 3 weeks | p Values pretreatment vs. 2 months |
|-----------------------|--------|---------------|----------------|-------------------------------|-------------------------------|
| Tear meniscus height (µm) | 279.0 ± 123.2 | 380.5 ± 174.7* | 317.0 ± 125.5* | <0.001* | 0.02* |
| Tear meniscus depth (µm) | 183.7 ± 59.7 | 235.7 ± 91.1* | 209.8 ± 77.1* | <0.001* | 0.015* |
| Tear break-up time (s) | 6.0 ± 4.3 | 6.3 ± 4.5 | 6.1 ± 3.8 | 0.6 | 0.6 |
| Corneal fluorescein staining | 1.7 ± 2.1 | 2.6 ± 3.3 | 2.3 ± 2.6 | 0.2 | 0.06 |
| Schirmer test (mm) | 7.8 ± 5.7 | 7.8 ± 5.3 | 6.9 ± 5.3 | 0.8 | 0.4 |
| OSDI score | 29.6 ± 25.3 | 19.8 ± 20.2* | 19.4 ± 21.7 | 0.03* | 0.09 |

OSDI Ocular surface disease index

*Clinically significant (p < 0.05)
the lacrimal pump and increases tear retention due to paralysis of the orbicularis muscle [26, 27]. Ho et al. showed that lipid tear thickness is significantly increased, without any change in meibomian gland dropout, when compared to baseline at the first month of BTX-A treatment. They concluded that this effect

Table 2 Changes in corneal topography and corneal aberrations after BTX-A injections in patients with blepharospasm and hemifacial spasm

| Variables (mean ± SD) | Before | 3 weeks | 2 months | p Values pretreatment vs. 3 week | p values pretreatment vs. 2 months |
|-----------------------|--------|---------|----------|----------------------------------|-----------------------------------|
| K1                    | 43.15 ± 1.6 | 43.0 ± 1.5 | 43.1 ± 1.6 | 0.6                              | 0.1                              |
| K2                    | 43.9 ± 1.7  | 43.7 ± 1.6* | 44.0 ± 1.6 | 0.03*                            | 0.7                              |
| Kmean                 | 43.5 ± 1.6  | 43.3 ± 1.6  | 43.5 ± 1.6 | 0.07                             | 0.2                              |
| Thinnest corneal thickness (µm) | 541.8 ± 30.6 | 544.6 ± 28.08 | 543.9 ± 28.4 | 0.3                              | 0.06                             |
| Astigmatism           | 0.8 ± 0.5   | 0.6 ± 0.4*  | 0.8 ± 0.5  | 0.04*                            | 0.5                              |
| Spherical aberration  | 0.39 ± 0.13 | 0.4 ± 0.14  | 0.39 ± 0.15 | 0.4                              | 0.6                              |
| Vertical coma         | 0.06 ± 0.2  | 0.09 ± 0.2  | 0.10 ± 0.2 | 0.4                              | 0.2                              |
| Horizontal coma       | −0.02 ± 0.1 | −0.04 ± 0.1 | −0.05 ± 0.15 | 0.9                             | 0.3                              |
| Higher order RMS      | 0.67 ± 0.21 | 0.65 ± 0.22 | 0.65 ± 0.19 | 0.5                              | 0.9                              |
| Total RMS             | 2.49 ± 1.0  | 2.43 ± 1.3  | 2.5 ± 1.1  | 0.6                              | 0.8                              |

K1 Corneal power of flat axis, K2 corneal power of steep axis, Kmean mean corneal power, RMS root mean square

*Clinically significant (p < 0.05)

Table 3 Changes in the tear and ocular surface parameters in the contralateral eyes of hemifacial spasm patients

| Variables (mean ± SD) | Before | After 3 weeks | After 2 months | p Values pretreatment vs. 3 weeks | p Values pretreatment vs. 2 months |
|-----------------------|--------|---------------|----------------|----------------------------------|-----------------------------------|
| Tear meniscus height (µm) | 347.8 ± 139.2 | 343.5 ± 117.1 | 330.2 ± 131.4 | 0.8                              | 0.6                              |
| Tear meniscus depth (µm)   | 238.4 ± 85.1  | 238.5 ± 73.2  | 220.0 ± 87.5  | 0.9                              | 0.5                              |
| Tear break-up time (s)      | 7.2 ± 4.3    | 6.4 ± 5.3     | 6.5 ± 5.0     | 0.2                              | 0.2                              |
| Corneal fluorescein staining | 1.0 ± 2.0    | 0.5 ± 1.1     | 1.1 ± 2.3     | 0.3                              | 0.9                              |
| Schirmer test (mm)           | 10.5 ± 6.5   | 7.9 ± 4.3     | 7.2 ± 5.6*    | 0.06                             | 0.008                            |

Table 4 Changes in corneal topography and corneal aberrations in the contralateral eyes of hemifacial spasm patients

| Variables (mean ± SD) | Before | 3 weeks | 2 months | p Values pretreatment vs. 3 week | p values pretreatment vs. 2 months |
|-----------------------|--------|---------|----------|----------------------------------|-----------------------------------|
| K1                    | 43.2 ± 1.6 | 43.2 ± 1.7 | 43.2 ± 1.6 | 1.0                              | 0.9                              |
| K2                    | 44 ± 1.7  | 43.9 ± 1.7  | 43.9 ± 1.6  | 0.4                              | 0.9                              |
| Kmean                 | 43.7 ± 1.6  | 43.6 ± 1.6  | 43.6 ± 1.6  | 0.5                              | 0.7                              |
| Thinnest corneal thickness (µm) | 546.7 ± 24.8 | 549.0 ± 28.0 | 546.8 ± 26.7 | 0.7                              | 0.2                              |
| Astigmatism           | 0.69 ± 0.4  | 0.68 ± 0.5   | 0.7 ± 0.4    | 0.5                              | 0.3                              |
| Spherical aberration  | 0.35 ± 0.12 | 0.38 ± 0.10  | 0.37 ± 0.10  | 0.2                              | 0.3                              |
| Vertical coma         | 0.06 ± 0.2  | 0.07 ± 0.2   | 0.04 ± 0.1   | 0.4                              | 0.8                              |
| Horizontal coma       | −0.03 ± 0.2 | 0.006 ± 0.2  | 0.001 ± 0.2  | 0.2                              | 0.4                              |
| Higher order RMS      | 0.60 ± 0.18 | 0.62 ± 0.21  | 0.57 ± 0.19  | 0.3                              | 0.2                              |
| Total RMS             | 1.95 ± 0.55 | 2.08 ± 0.54  | 1.90 ± 0.55  | 0.2                              | 0.8                              |

K1 Corneal power of flat axis, K2 corneal power of steep axis, Kmean mean corneal power, RMS root mean square
is due to paralysis of the lacrimal pump and the retention of tears on the ocular surface [28].

Lu et al. showed that inflammation related cytokines, like TNF-α, IL-6 and IL-1β, are higher in patients with BEB and DED compared to patients with only DED. The authors concluded that blinking in BEB patients leads to micro abrasive effects in the conjunctiva and increases inflammation [5]. According to the TFOS DEWS II report, tear film thickness is one of the dry eye sub-classification methods, and the tear film is composed of two layers; the mucous gel layer underneath, and an overlying lipid layer [29]. OCT measures the height, area and curvature of the upper and lower menisci and, although these parameters do not show the central tear film, the lower tear meniscus height shows the mucous tear volume [12, 30, 31]. In this study, TMH and TMD were significantly increased 3 weeks and 2 months after BTX-A treatment and OSDI scores, which evaluate the patients’ symptoms, decreased significantly at third week. TMH and TMD correlate well with dry eye symptoms [32]. Gunes et al. and Lu et al. also reported a significant decrease in OSDI scores after BTX-A injections in BEB and HFS patients [5, 9]. Despite the improvement in OSDI scores, there were no significant changes in TBUT, Schirmer I or CFSS. This finding can be related to the increase in inflammatory mediators on the ocular surface and can be explained by the poor correlation between dry eye symptoms and signs including the Schirmer test and ocular staining, as reported previously [33].

In the present study, TMH and TMD increased significantly after BTX-A injection. In a recent study, Park et al. evaluated lacrimal drainage and TMH in BEB patients and showed an increase in TMH and tear clearance time after BTX-A treatment [4]. The results of these studies suggest that BTX-A related paralysis of the orbicularis muscle leads to a decrease in nasolacrimal outflow and tear retention.

Eyelid pressure is an important cause of corneal astigmatism. Previous studies have reported corneal topographic changes after ptosis, blepharoplasty and gold-weight implant surgery [34, 35]. Gunes et al. evaluated corneal topographic changes after BTX-A treatment in HFS and BEB patients and reported a significant decrease in astigmatism [9]. Similarly, Osaki et al. reported that steep keratometry and astigmatism decreased significantly at 2 months and 3 months after treatment in HFS patients [36]. While the decrement in steep K and astigmatism values was statistically significant 3 weeks after BTX-A injections, the change between the baseline and 3rd week measurements (0.2 D for the steep K) was very close to the repeatability limits of Pentacam [37].

In the present study, the changes in anterior corneal aberrations after BTX-A treatment were also investigated. Previous studies have shown that abnormalities in the tear film and an increase in the inter-blink interval increase corneal and total aberrations and affect visual quality [38–41]. It is reported that the progression index of corneal HOAs correlated with the OSDI scores and ocular symptoms [19]. In a study comparing ocular wave front aberrations of normal and dry eyes, spherical-like and coma-like higher order aberrations were significantly greater in dry eyes [42]. It has been shown that SA, vkoma, hkoma and HOA of the anterior cornea, decrease after 2 weeks instillation of artificial eye drop in dry eye patients. Isshiki et al. evaluated total ocular aberration and reported a significant decrease in HOA in BEB patients after relieving spasms [17]. Yakibu et al. reported a significant decrease in total hRMS and SA after treatment in BEB and HFS patients [18]. This is the first study to evaluate anterior corneal aberrations after BTX-A injections in patients with BEB and HFS. In this study, there were not any difference in between corneal aberrations before and after BTX-A injections. The difference between these results may be explained by the difference in the measured aberrations, that is, ocular versus corneal. Also, although the tear meniscus increased and OSDI scores decreased, no significant improvement was observed in Schirmer test, TBUT and corneal fluorescent staining. In the control group Schirmer test score decreased at 3 weeks and 2 months after BTX-A injection and the difference between before and after 2 months were clinically significant. Higher Schirmer test results before treatment in control eyes can be explained by increased reflex tearing due to frequent blinking on the spasm side. Jariyakosol et al. showed no differences in Schirmer test results between before and after BTX-A treatment in control eyes of HFS patients [43].

There are some limitations of this study. Firstly, the number of participants is low and, secondly, all patients included in the study had undergone long-term BTX-A treatment (mean number of
visits/patient 15.3 ± 11.2)). As the action of BTX-A in the literature for BEB and HFS is reported 2–4 months [22, 44], the previous BTX-A effect may not be completely over in all participants at the time of enrollment for the study (average time between the last and current BTX-A injection was 3.8 ± 0.8 months). Also long-term BTX-A treatment may cause impairment of ocular surface other than the facial dystonies themselves [7, 45].

Finally, tear function tests should ideally be performed prior to invasive procedures, since we completed the Schirmer test first, the inclusion of anesthetic drug and ocular irritation caused by the strip might change tear structure and tear stability and might have affected TBUT and CFSS results.

In conclusion, BTX-A treatment seems to induce a significant reduction in symptoms related to DED. However the positive effects of BTX-A treatment on ocular surface tended to reduce during the period of action of BTX-A.

Author’s contributions Dr. Bayraktar Bilen—Data collection, manuscript submission and coordination, statistical analysis; Dr. Bilen—Coordination and data collection; Dr. Topçu Yılmaz—Data and Manuscript Editing; and Evren Kemer—Consultants to the procedure.

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Data availability The manuscript has no associated data in a data repository.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ankara Numune Education and Research Hospital E-19-2606) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Animal research This article does not contain any studies with animals performed by any of the authors.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Informed consent for potential research publication was obtained from all individual participants included in the study at the time of their treatments performed.

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