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ORIGINAL PAPER

Nonsurgical treatment for upper eyelid retraction in patients with inactive Graves' orbitopathy

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Abstract

Purpose To evaluate the effectiveness of incobotulinumtoxinA (Xeomin®) in treating upper eyelid retraction in patients with Graves orbitopathy (GO) initially scheduled for surgery via two different application sites.

Methods This is a comparative, prospective study, conducted at the Department of Ophthalmology, Medical School, University Hospital Centre Zagreb, EUGOGO site (EUropean Group On Graves' Orbitopathy) in Croatia from January 2020 till January of 2021 in accordance with national health headquarter recommendations. All patients were classified as inactive with marked eyelid retraction and randomly divided into groups according to application sites. Group A underwent transconjunctival application (18 eyes) and group B transcutaneous application (20 eyes) of incobotulinumtoxinA. The primary end point of this study was lowering the eyelid, to alleviate anterior eye segment symptoms and achieve acceptable aesthetic appearance until surgery becomes available.

Results There were no nonresponders and we found no statistically significant difference in the degree of lowering the eyelid between the two application sites. Following rules for avoiding spread of SARS-CoV-19, none of the patients included in this study were infected. Moreover, participants reported diminishing of anterior eye segment irritation and improved aesthetics.

Conclusion Treatment of inactive GO patients with incobotulinumtoxinA for upper eyelid retraction is efficient and safe and can be used as an adjuvant treatment while patients wait for surgery, by alleviating symptoms and improving the level of aesthetic satisfaction without causing a threat to anterior eye segment and visual function.

The study showed that effect of treatment was the same, whether we applied the toxin transconjunctivaly or transcutaneously.

Keywords incobotulinumtoxinA · Xeomin® · upper eyelid retraction · Graves' disease · Graves' orbitopathy

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Introduction

Thyroid-associated orbitopathy (TAO), also known as Graves' orbitopathy (GO), is the most common autoimmune disease of the orbit and primarily affects periocular tissues with secondary effect on the eye and psychosocial functioning of the patient. Although the disease is more common in women, the proportion of men increases as severity does. The most frequent sign in GO is eyelid retraction, which affects 90–98% of patients [1]. Retraction frequently varies with attentive gaze, a phenomena called Kocher's sign. Contour of the retracted upper eyelid often shows "lateral flare", an appearance that is almost pathognomonic for the disease [2]. The aetiology of the eyelid retraction is multifactorial and is due to increased sympathetic stimulation of Muller's muscle, contraction of the levator muscle, and scarring between the lacrimal gland fascia and levator, which specifically gives rise to the "lateral flare" and is often exacerbated by involvement of inferior rectus due to Hering's law. The excursion of the upper eyelid often lags behind eyeball movement on vertical downward pursuit (lid lag) and remains high. This phenomenon is called von Graefe sign. Due to tissue swelling, patients have eyelid oedema and erythema, proptosis and in severe cases, with incomplete eyelid closure, the lagophthalmos. Inflammatory and post-inflammatory changes of the muscles cause diplopia. Most patients develop anterior eye segment exposure symptoms (foreign body sensation, grittiness, photophobia and lacrimation). Although inflammation on the ocular surface is recently recognized as the precursor of circulus vitiosus that will occur on the cornea and bulbar conjunctiva in patients with GO [3], secondary changes like wide palpebral aperture combined with poor blinking will have significant worsening impact on the symptoms of dysfunctional tear syndrome [4] especially in patients with inactive GO. Twenty per cent of patients indicate that the ocular morbidity of this condition is more troublesome than the systemic complications of thyroid function impairment [5].

Due to the self-limiting course of the disease, correction of eyelid position with botulinum toxin A reduces frightened appearance and improves aesthetic satisfaction and also acts protectively on the anterior ocular segment while waiting for the disease to subside or for surgical procedures to be undertaken.

Following rules for avoiding spread of SARS-CoV-19, none of the patients included in this study were infected. Moreover, participants reported diminishing of anterior eye segment irritation and improved aesthetics.

Botulinum toxin (BoNTA) has been used for eyelid retraction treatment for almost thirty years [6–8]. In previous studies the toxin was administered by either subconjunctival [9–11] or transcutaneous approach [12–14] and in both inflammatory and fibrotic stage [15].

Sadiq et al. did the comparisons of the incidence of reduced upgaze in trascutaneous versus transconjunctival administration of BTXA (Dysport) to induce protective ptosis in patients with exposure keratopathy due to facial nerve palsy [16], but in the literature review we did not find the comparison of these two application approaches on the degree of eyelid lowering.

The aim of the present study was to investigate the overall effect of incobotulinumtoxinA in patients with inactive GO and to see whether the site of application of BoNTA has the effect on lowering the eyelid in patients with CAS less than 3. We used a purified type of botulinum toxin, incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt) which was shown to be as effective as on abotulinumtoxin A (Botox®) with a comparable adverse event profile when a clinical conversion ratio of 1:1 is used [17–20] and was shown to be less immunogenic than other commercially available BoNT/A formulations [21].

Subjects and methods

A total of 28 patients (38 eyes) with Graves orbitopathy and CAS lesser than 3 with upper eyelid retraction were divided into 2 groups: group A with transconjunctival application (18 eyes) and group B with transcutaneous application (20 eyes).

Follow-up for all patients was 6 months: initial examination before treatment and one, six and twenty-four weeks after the application.

At each visit, patients underwent ophthalmological examination of both eyes which included: visual acuity check, slit lamp examination with Goldman applanation tonometry in primary position and elevation.

We evaluated the activity of Graves orbitopathy by clinical activity score (CAS). MRD1 and 2 were recorded as well as levator function, Hertel exophtalmometry, height of lateral flare, von Graefe sign and lagophtalmos. Corneal fluorescein staining (CFS) was performed to all patients on each visit.

Additional evaluation performed at strabology unit included ductions and versions, Hess-Lancaster test and photo-documentation of the face. The examinations were taken in the same office by two ophthalmologists in different appointments.

Due to fluctuations in the position of the retracted upper eyelid, each measurement regarding lid position was done 3 times and the average result was recorded.

Margin reflex distance 1 or MRD1 is determined by the examiner and patient aligning at the same level. A light is directed at the patient's eyes. The MRD1 is the measurement in millimetres from the light reflex on the patient's cornea to the level of the centre of the upper eyelid margin, with the patient gazing in the primary position. MRD1 is used to indicate degree of ptosis or retraction. Normal distance is 4–5 mm.

Margin reflex distance 2 or MRD2 measures from the corneal light reflex to the central portion of the lower eyelid, with the patient's eyes in the primary gaze. Normal distance is 4–5 mm.

Central palpebral fissure height is the sum of the values of MRD1 and MRD2 measured centrally and temporal.

Palpebral fissure height is the sum of the values of MRD1 and MRD2 measured at limbus temporally.

Levator function (upper eyelid excursion): The distance from the upper eyelid margin in downgaze to upgaze with frontalis muscle function neutralized. Normal eyelid excursion is 12–17 mm.

Potential major complications: ptosis, diplopia, symptoms of dry eye, visual disturbances and minor complications: post-applicational haematoma and prolonged post-applicational discomfort were also recorded.

The second part of the evaluation process was filling out a questionnaire concerning GO and its impact on patient's life.

We designed a questionnaire for the patients to see whether the treatment, in addition to lowering the eyelid, changed the incidence of other symptoms of orbitopathy: watery eyes, grittiness, retrobulbar pressure and pain and how much did the treatment changed the feeling of satisfaction with the appearance, especially when wearing masks attracted extra attention to the eyes. We were also interested if patients smoked, what kind of thyroid disorder they had and what was the hormonal status during the study, which forms of treatment for the acute phase of orbitopathy they have underwent, and how long the duration of eyelid retraction was.

IncobotulinumtoxinA is a sterile white to off-white lyophilized powder which was reconstituted with preservative-free 0.9% sodium chloride solution in form 1:4 in our study.

The patients were administered different doses of incobotulinumtoxinA, depending on the degree of upper eyelid retraction. Doses varied from 2.5 U per eye to 15 U. The degree of eyelid retraction was measured by MRD1 in mm and for each mm of eyelid lowering that we wanted we applied 2.5 U of diluted toxin. In group A with transconjunctival application (18 eyes), we applied of total amount of 110 U and in group B with transcutaneous application (20 eyes) total amount of 122.5 U of toxin. The most frequent doses that we used were 7.5 U (in 6 patients in both group A and group B) and 5 U (in 8 patients in group A and 9 patients in group B). In cases of bilateral retraction, we always used both methods and the eye was chosen randomly.

In a transconjunctival application group, the upper eyelid was everted and the incobotulinumtoxinA was injected subconjunctivaly on the level of upper tarsal border in temporal part of the eyelid.

In transcutaneous application group, the Jäger plate was placed beneath the upper lid and the incobotulinumtoxinA was administered through the orbital septum in temporal part of supratarsal crease (Fig. 1).

After each application, the patients were asked to give procedure pain assessment on the scale form 1 (no pain) to 5 (very severe).

Results

The main effect of incobotulinumtoxinA applied to the eyelid is decrease in vertical palpebral height due to lowering of the upper eyelid. Unlike majority of previous studies where the same amount of incobotulinumtoxinA was applied regardless of the severity

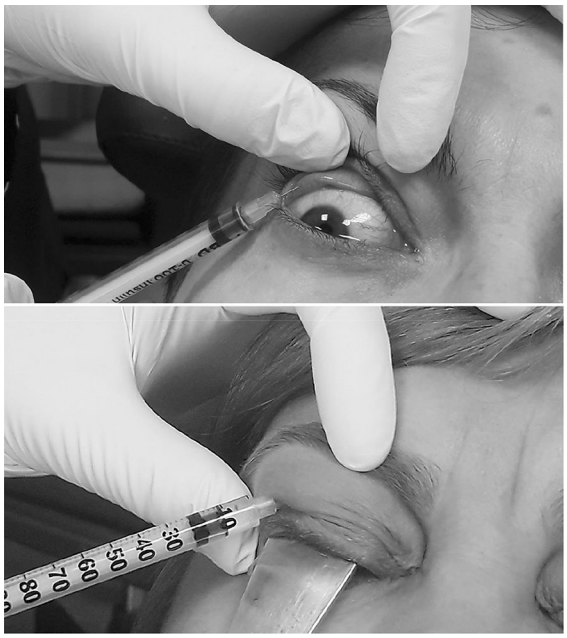

Fig. 1 Transconjunctival and transcutaneous application of incobotulinumtoxinA

of the retraction, we adjusted the dose for each eye depending on the severity of the retraction (Figs. 1 and 2).

For statistical reasons, we calculated the difference between the average measures taken before application and on first visit one week after, and the second visit six weeks after treatment and divided them with the number of U that we used. Using this formula, enabled comparison of the effect of one U of incobotulinumtoxinA used through two different anatomical sites.

It is obvious that incobotulinumtoxinA caused eyelid lowering, decrease in central and temporal palpebral fissure height and levator function on each visit (Table 1).

Although some differences are observed in the graph, by using the *t*-test in order to check the difference in effects between the two types of application sites, we found that there is no statistically significant difference (Figs. 3, 4 and 5).

Major complications: ptosis, diplopia, symptoms of dry eye, visual disturbances and minor: post-applicational haematoma and prolonged post-applicational discomfort are shown in Fig. 6 and Table 2.

There were no statistically significant differences using the Chi-square test except for measurements after 6 weeks in the dry eye variable ($\chi^2 = 5.71$; df = 1; $p = 0.02$). After 6 weeks, the dry eye was significantly more present (33.3%) in transconjunctival application group than in transcutaneous application group (13.3%).

Incidence of complications changes over time showed no statistical difference in transconjunctival application group, whereas in transcutaneous application group we had statistically significant higher incidence of post-applicational ptosis (50% vs. 6.7%) after 1 week compared to the examination after 6 weeks ($\chi^2 = 6.81$; df = 1; $p < 0.009$).

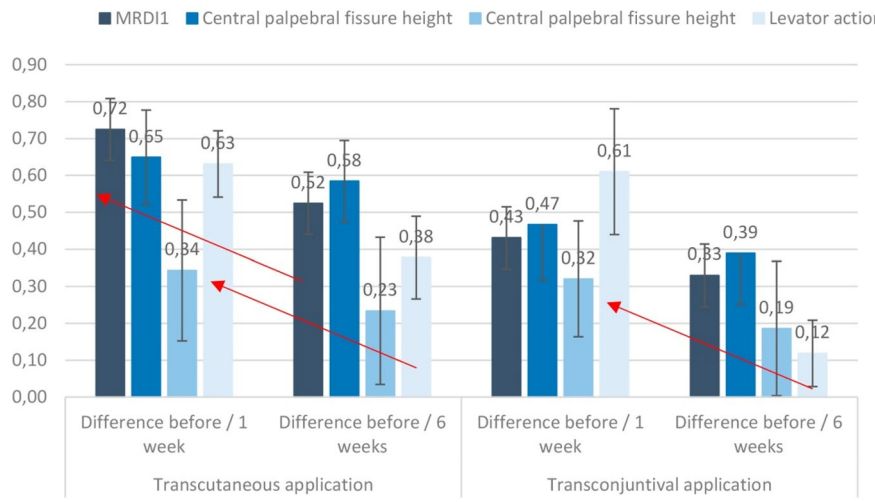

Fig. 2 The effect of 1 U of incobotulinumtoxinA on observed parameters expressed in mm after 1 week and 6 weeks for each method of application

Table 1 Difference in the effect of two methods on observed parameters between visits

	t-test*	df**	*p****
Difference in mrd1 before application and 1 week after application / number of units	− 1.97	26	0.059
Difference in mrd1 before application and 6 weeks after application / number of units	− 1.39	22	0.178
Difference in central palpebral fissure height before application and 1 week after application / number of units	− 0.93	26	0.361
Difference in central palpebral fissure height before application and 6 weeks after application / number of units	− 1.10	22	0.284
Difference in temporal palpebral fissure height before application and 1 week after application / number of units	− 0.09	22	0.931
Difference in temporal palpebral fissure height before application and 6 weeks after application / number of units	− 0.15	20	0.883
Difference in levator function before application and 1 week after application / number of units	− 0.11	26	0.911
Difference of levator function before application and 6 weeks after application / number of units	− 1.61	22	0.121

**t*-test: in millimetres difference

***df*: degrees of freedom

****p*: *t*-test *p* value

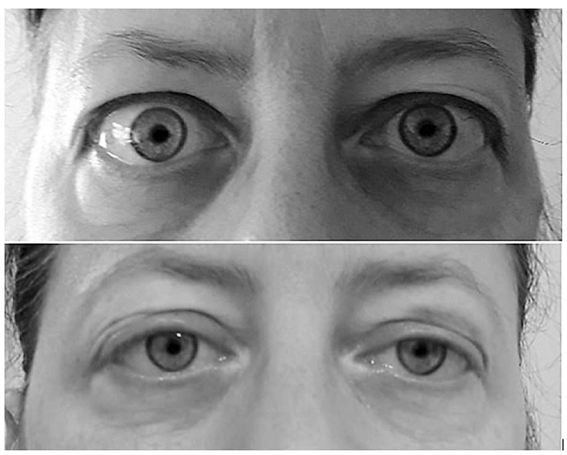

Fig. 3 Before and after picture of patient treated with 10 U of incobotulinumtoxinA in the right eyelid transconjunctivaly and 7.5 U in the left eyelid transcutaneously

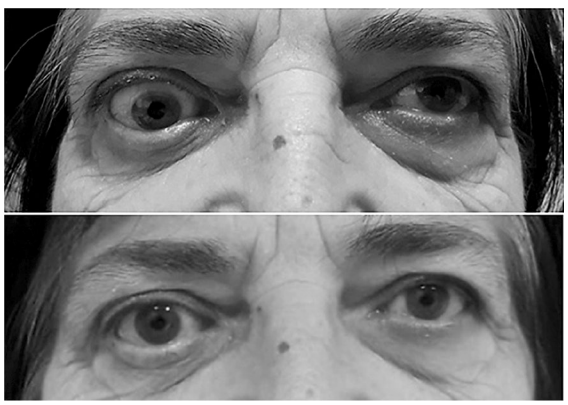

Fig. 4 Before and after picture of patient treated with 5 U of incobotulinumtoxinA in the right eyelid transcutaneously

Patients reported that overcorrection spontaneously disappeared within first month after treatment (25 ± 3 days).

Some of our patients had diplopia before treatment, often intermittent, as a result of the disease. None of them had serious worsening of diplopia after treatment that would impact everyday life and that would need additional treatment. Minor transient complication, hematoma, has occurred slightly more often in transcutaneous application group without causing a stress to the patients. No evidence of vision impairment on the Snellen plates was recorded.

Specially designed questionnaire included questions on the presence of ocular symptoms found in GO: watery eyes, grittiness, retrobulbar pressure and eyelid pain. Given the sample, there were no statistically significant differences using the Chi-square test to occurrence of those subjective complaints between two application groups after six weeks (Table 3).

We achieved really satisfying degree of aesthetic approval in both application groups. After 6 weeks, we had 73.3% satisfied patients in transcutaneous application group and 55.6% in transconjunctival application group and found no statistically significant differences. Overall satisfaction improved

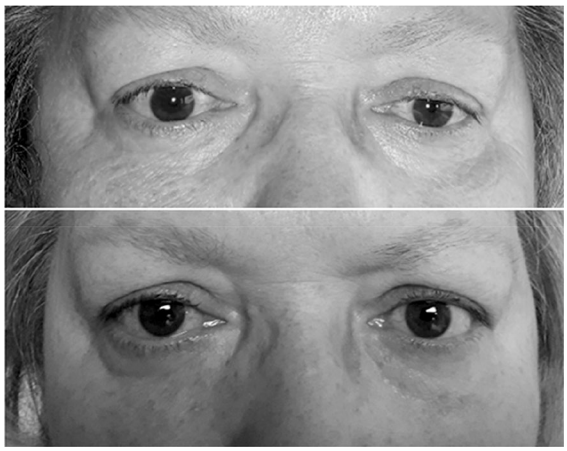

Fig. 5 Before and after picture of patient treated with 2.5 U of incobotulinumtoxinA in the right eyelid transcutaneously

occurred regardless to that the other aspects of GO did not change.

In this study, 88% of patients were female average age of 50 yrs (± 20), 11% of them were smokers, refractive to information on detrimental effect of smoking on GO given at each check-up. Duration of the retraction before application was in average 59 months (± 10 months), 44% patients during active phase of disease underwent other forms of GO treatment, including intravenous corticosteroid therapy, orbital radiotherapy and orbital decompression surgery. Primary thyroid disease was present in 78% hyperthyroidism, 18% of patients were hypothyroid, and 4% were euthyroid. There was no significant difference in response to incobotulinumtoxinA application between those who were previously treated and those who were followed by "wait and see" policy. Also, thyroid status had no impact on incobotulinumtoxinA response.

There is no statistically significant difference in the pain level during procedure for these two application groups, either. Patients describe it more as a discomfort than a real pain. Average grade for transcutaneous application is 2.08 and for transconjunctival 2.44 on our procedure pain assessment scale graduated from 1 (no pain) to 5 (very severe) ($t = 0.82$; $df = 20$; $p = 0.420$). As the effect was worn off between check-ups, patients gave us information regarding the duration of treatment effect with which they were satisfied on last visit, six months after treatment. There was a statistically significant difference in the two application groups. Patients were satisfied with eyelid position one month longer in transcutaneous versus transconjunctival application group ($t = -2.63$; $df = 10$; $p = 0.025$).

Discussion

The main limitations of this study are small number of patients and great intervals between follow-up examinations which were mutually agreed upon because of this extraordinary pandemic circumstances. The results showed that we can use Xeomin® to treat upper eyelid retraction as previous studies have shown for other forms of botulinum toxin

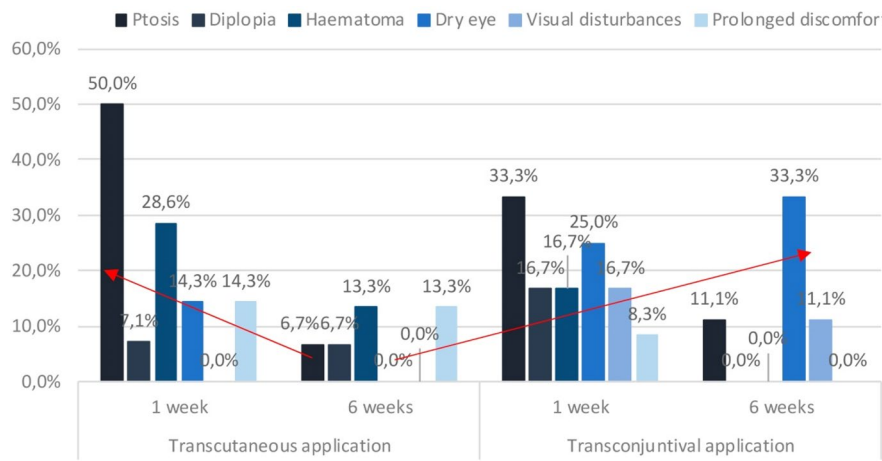

Fig. 6 Incidence of complications on each visit for both methods of application

Table 2 Change in incidence of complications for both applications between visits

	1 week after application (%)	6 weeks after application (%)	Chi-square test	df*	*p***
Transconjunctival application					
Ptosis	33.3	11.1	1.40	1	0.237
Diplopia	16.7	0.0	1.66	1	0.198
Haematoma	16.7	0.0	1.66	1	0.198
Dry eye symptoms	25.0	33.3	0.18	1	0.676
Visual disturbances	16.7	11.1	0.13	1	0.718
Prolonged discomfort	8.3	0.0	0.79	1	0.375
Transcutaneous application					
Ptosis	50.0	6.7	6.81	1	0.009
Diplopia	7.1	6.7	0.00	1	0.956
Haematoma	28.6	13.3	1.03	1	0.311
Dry eye symptoms	14.3	0.0	2.30	1	0.129
Visual disturbances	0.0	0.0	0.00	1	1.000
Prolonged discomfort	14.3	13.3	0.01	1	0.938

*df: degrees of freedom

***p*: hi square *p* value

(Botox®, Dysport®) and with this number of patients, we found no difference in the effect between two applications.

As the effect has worn off between check-ups, patients gave us information regarding the duration of treatment effect with which they were satisfied on their last visit, six months after treatment. Considering that none of our patients had worsening in the GO activity in such a short period of time and we lowered the eyelid, so the evaporation of tears should diminish, it could be concluded that the worsening of dry eye in a transconjunctival application group could be consequence of the toxin application. Studies have shown that the pericular application of toxins in e.g. aesthetic treatments and in the treatment of blepharospasm worsens dryness of the eye by blocking the parasympathetic transmission in the lacrimal gland; it is to be expected that the application in the temporal part of the eyelid can also affect the work of the lacrimal gland by diffusion of the toxin [22]. This should definitely be further investigated with larger number of patients.

Conclusion

Treatment with incobotulinumtoxinA for upper eyelid retraction is both safe and efficient, whether we apply it transconjunctivaly or transcutaneously. It is a modality of treatment prior to surgical correction or when surgery is not an option. It significantly improves quality of life by improving patient's periocular status and lifting the level of aesthetic satisfaction. The data showed that a slight hypercorrection one week after transcutaneous application especially when using a larger number of U might be expected, but post-application ptosis disappeared spontaneously within first month since treatment. The patients were satisfied with treatment effect for 5 months in transcutaneous group and one month less in transconjunctival group. Transconjunctival application seems to be more appropriate to treat milder forms of retraction. In these patients, it is necessary to carefully monitor the signs of dryness of the anterior eye segment, as

Table 3 Difference in subjective complaints after six weeks between both methods of application

	6 weeks after applications		
	Chi-square test	df*	*p***
Watery eyes	0.12	1	0.728
Grittiness	1.60	1	0.206
Retrobulbar pressure	0.63	1	0.429
Pain	1.55	1	0.214
Aesthetic satisfaction	0.80	1	0.371

*df: degrees of freedom

***p*: hi square *p* value

we found that symptoms of dry eye are statistically more pronounced after six weeks post-treatment in this group.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sandra Vokurka Topljak, Martina Galiot Delić and Sanja Perić, review and editing Krešimir Mandić, Maja Baretić and supervision Jelena Juri Madić. The first draft of the manuscript was written by Sandra Vokurka Topljak and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have not disclosed any conflict of interests.

Ethics approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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

Consent to publish Patients signed informed consent regarding publishing their data and photographs.

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