Alterations of Corneal Dendritic Cell Density After Pattern Scanning Laser Trabeculoplasty in Open Angle Glaucoma

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ABSTRACT

Purpose: To evaluate the effect of Pattern Scanning Laser Trabeculoplasty (PSLT) procedure on corneal subbasal nerve density (SND) and dendritic cell density (DCD) in refractory open-angle glaucoma cases with the help of in vivo confocal microscopy (IVCM).

Materials and Methods: This is a prospective cohort study of 15 eyes of 15 patients with various types of open-angle glaucoma that were treated with single session of PSLT. Patients demographic characteristics, type of glaucoma, and necessity of antiglaucoma treatments were evaluated. After full ophthalmological examination, IVCM was performed before and after PSLT. Follow-up visits were at 1 day, 1 week, 1 month.

Results: The mean age of the participants included in the study was 68.13±11.58 (56-86) years. According to glaucoma types; 53.3% of the participants were primary open-angle glaucoma, 40.0% were pseudoexfoliative glaucoma, and 6.7% were steroid induced glaucoma. There was no statistically significant difference between the SND values of pre-procedure, post-procedure 1st day, post-procedure 1st week, post-procedure 1st month. Post-procedure 1st day DCD values increased significantly compared to pre-procedure, the increase continued in the 1st week, and the difference disappeared by the 1st month. There was no significant difference in terms of both SND and DCD values before and after the procedure.

Conclusions: The increase in DND, after a single dose of PSLT, was reverted to baseline values as of the 1st month. This may be a biomarker that shows PSLT efficacy as well as the severity of the inflammatory state.

Keywords: Glaucoma, Selective laser trabeculoplasty, Pattern scanning laser trabeculoplasty, In vivo confocal microscopy, Dendritic cell density.

INTRODUCTION

Glaucoma is a multifactorial, progressive optic neuropathy which is the second cause of blindness worldwide after cataract.[1] The main goal of glaucoma treatment is to halt the progression of disease and vision loss by lowering intraocular pressure. In addition to medical treatment, laser treatment options and surgical methods form the basis of glaucoma treatment.

Selective laser trabeculoplasty (SLT), which increases aqueous outflow by creating photothermolysis at the cellular level, has now become an accepted treatment option in cases of open-angle glaucoma and ocular hypertension.[2] Pattern Scanning Laser Trabeculoplasty (PSLT) is a semi-automatic photocoagulation method introduced in 2006, it performs selective photothermolysis, remodeling the trabecular meshwork and increasing aqueous outflow, similar to SLT in terms of working principle. Comparing with SLT, it provides short pulse duration (10-20 ms), a spot width of 100 µm, thus reducing thermal damage to the surrounding tissue by providing more shots per area in the trabecular meshwork.[3-5]

Corneal changes such as transient reduction in corneal endothelial cell count, corneal edema, corneal clouding, corneal thinning, keratitis, hyperopic or myopic shift after SLT have been described in previous studies and it has

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been suggested that inflammation is the prominent cause of all these alterations.[6-9]

Corneal subbasal nerve density (SND) and dendritic cell density (DCD); both are significant biomarkers for ocular inflammation after laser trabeculoplasty and can be detected non-invasively with the help of in vivo confocal microscopy (IVCM).[10]

In this study, it was aimed to evaluate the effect of PSLT on subbasal nerve density and dendritic cell density in refractory open-angle glaucoma cases with the help of in vivo confocal microscopy.

MATERIALS AND METHODS

Subjects:

This is a prospective cohort study of 15 eyes of 15 patients with various types of open-angle glaucoma that were treated with single session PSLT. Informed patient consent was obtained before study commencement. Primary open-angle glaucoma (POAG) was described as a glaucomatous- appearing optic nerve (neuroretinal rim thinning or notching), retinal nerve fiber layer (RNFL) thinning on optic coherence tomography (OCT) (Zeiss Cirrus HD-OCT, Zeiss Meditec. Inc, Germany) outside the 95% confidence interval of the normal distribution, and a glaucomatous visual field defect on 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard perimetry. Pseudoexfoliation glaucoma (PXG) was described as exfoliation material on biomicroscopic examination with a glaucomatous- appearing optic nerve, RNFL thinning on OCT outside the 95% confidence interval (CI) of the normal distribution, and a glaucomatous visual field defect on 24-2 SITA standard perimetry.

Inclusion criteria were: Being refractory to antiglaucoma drugs, having drug incompliance or not accepting the surgical treatment offer as an option. Newly diagnosed glaucoma cases without medication, patients with preexisting corneal pathology, corneal scar, endothelial cell density below 1000 cells/mm^2, previous laser trabeculoplasty treatment and surgeries or systemic diseases such as diabetes, rheumatological diseases that may affect corneal inflammation were excluded. Ethical approval was obtained from the Mugla University School of Medicine Ethical Committee (No:13/X, Date:03.12.2020)

Data Collection:

Patients demographic characteristics, type of glaucoma, and necessity of antiglaucoma treatments were evaluated. After topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine, Alcon, Fort Worth, Texas, USA) drip, IVCM was performed using the Rostock corneal module with the HRT III (Heidelberg Engineering GmbH, Heidelberg, Germany) device. A diode laser source that provides red light at a wavelength of 670 nm was internally mounted on the HRT.

Before procedure, a drop of Viscotears gel (Alcon Laboratories, Inc., Texas, USA) was placed in and on the TomoCap (Heidelberg Engineering) in the microscope objective. The tip of the TomoCap was brought into contact with the patient's cornea and the patient was asked to look at a fixed point. The best 3 images obtained from the central cornea were evaluated and averaged. High-resolution real-time images consist of 384x384 pixels covering an area of 400x400mm with a resolution of 1 mm/pixel were obtained.

Nerve density was measured using the NeuronJ (National Institutes of Health, Bethesda, MD, USA) plug-in from ImageJ software, which allows semi-automatic tracking and quantification of nerve fibers. Dendritic cells were differentiated due to their bright cell bodies and counted manually in the subbasal nerve plexus using ImageJ software. Two masked experienced researchers analyzed the well-focused images for corneal nerve morphologic features and investigated the density of nerve fibers. (A.K. and H.C.Ş)

Follow-up visits were at 1 day, 1 week, 1 month. All intraocular pressure measurements consisted of three readings using Goldmann applanation tonometry, and the average was used in data analysis. Tonometers were calibrated every 3 months.

Laser treatment procedure:

PSLT was performed using the Pascal laser (PAS- CAL Streamline 577; Topcon Inc., Tokyo, Japan). All 15 eyes received a single session of 360° laser treatment. A Goldmann three mirror goniolens (Volk, USA) was used to project and align laser patterns onto trabecular meshwork (TM). All patients received two drops of pilocarpine 2% prior to the procedure, and one drop of Brimonidine tartarate 0.15% immediately after, as well as a prescription of ketorolac tromethamine 0.5% (one drop qds for 4 days).

The energy level was titrated (starting from a 500 mW power and adjusted accordingly) by placing a single laser spot (100 µm diameter) in the inferior quadrant at 10-ms exposure duration until a barely blanching of the TM was obtained. Then, pulse duration was automatically reduced to 5 ms to produce subvisible lesions. PSLT delivered a total of 1248 pulses in 32 sequential segments. Each segment comprised 39 spots (13 columns x 3 rows) spanning 11.25° of the trabecular meshwork. The contact lens was rotated every 11.25° after a segment was treated and the procedure was repeated 32 times so that the trabecular meshwork was treated for 360° with no overlap and no gap of the treatment spots.

Statistical Analyses

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables were normal or not was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±SD for normal distributions, and median (interquartile range) for skewed distributions. Categorical data were described as number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t test. Statistical analysis differences in normally distributed variables between four dependent groups were compared by repeated measures anova test. It was evaluated degrees of relation between variables with pearson or spearman correlation analysis. It was accepted p-value <0.05 as significant level on all statistical analyses.

RESULTS

Fifteen eyes of 15 open angle glaucoma patients were evaluated. The mean age of the participants was 68.13±11.58 (56-86) years.. The mean central corneal thickness value was 550.73±41.71 µm (468-615). Any post-operative complication was not observed. (Table 1)

While the mean intraocular pressure value of all cases was 28.47±6.25 mmHg before the procedure, this value was 21.47±6.79 mmHg at 1 week after the procedure, and 18.00±6.79 (14-20) mmHg on 1st month. While the mean number of antiglaucomatous drugs used before the procedure was 3.27±0.96 (3-4), this value was 3.04±0.70 (3-4) on 1st week, and 2.40±1.40 on 1st month. According to the visual field test analysis, the mean MD values were 18.01±8.83, and the PSD values were 4.68±2.78. (Table 2)

Although there was no statistically significant difference between the SND values of pre-procedure, post-procedure 1st day, post-procedure 1st week, post-procedure 1st month (p= 0.147), statistically significant difference between the DCD values of pre-procedure, post-procedure 1st day, post-procedure 1st week, post-procedure 1st month was detected. (Table 3, Figure 1)

Post-procedure 1st day DCD values increased significantly compared to pre-procedure, the increase continued in the 1st week, and the values reverted the pre-procedure values by the 1st month. (Table 3, Figure 2)

There was no statistically significant difference between DCD values and the decrease in IOP. (Table 4)

DISCUSSION

PSLT, which can be chosen as the first interventional method before surgery in cases refractory to antiglaucomatous

Table 1: *Examination results of the participants according to age, gender, glaucoma type, central corneal thickness values, laterality, laser treatment degree and presence of complications*

		All cases (n:15)
Age		68.13±11.58
Gender	Male	12 (80.0%)
	Female	3 (20.0%)
Glaucoma Type	POAG	8 (53.3%)
	PEXG	6 (40.0%)
	Steroid induced	1 (6.7%)
Central corneal thickness (µm)		550.73±41.71
Laterality	Right	9 (60.0%)
	Left	6 (40.0%)
Complication		-

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q_1-Q_3) and categorical variables are expressed as either frequency (percentage).
POAG:primary open angle glaucoma, PEXG: pseodoexfoliative glaucoma

Table 2: *Characteristics of the participants according to intraocular pressure values, number of drugs used and visual field test results*

		All cases (n:15)
IOP	Baseline IOP	28.47±6.25
	1st w IOP	21.47±6.79
	1st m IOP	18.00±6.79 (14-20)
Number of medication	Baseline med	3.27±0.96 (3-4)
	1st w med	3.04±0.70 (3-4)
	1st m med	2.40±1.40
Mean MD		18.01±8.83
Mean PSD		4.68±2.78

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q_1-Q_3).
IOP: intraocular pressure, med: medication number, MD: mean deviation, PSD: pattern standard deviation, w: week, m:month

Table 3: *Comparison of subbasal nerve density and dendritic cell density values between Pre-procedure, post- procedure 1st day, post-procedure 1st week, post-procedure 1st month evaluations*

			Post Hoc Test					
		All cases (n:15)	**Before-1.day**	**Before-1.w**	**Before-1.m**	**1.day-1.w**	**1.day-1.m**	**1. w-1.m**
SND	Before	2814.73±498.09	-	-	-	-	-	-
	1st day	2740.73±540.60	-	-	-	-	-	-
	1st w	2767.00±491.58	-	-	-	-	-	-
	1st m	2751.80±465.60	-	-	-	-	-	-
	P value <0.001							
DCD	Before	10.20±2.62						
	1st day	15.40±3.58						
	1st w	16.33±2.77	**<0.001**	**<0.001**	0.999	0.872	**<0.001**	**<0.001**
	1st m	10.73±1.79						
	P value=0.143							

Continuous variables are expressed as the mean±standard deviation (SD). Continuous dependent variables were compared with repeated measures anova. Statistically significant p-values are in bold.
SND: subbasal nerve density, DCD: dendritic cell density, w: week, m: month

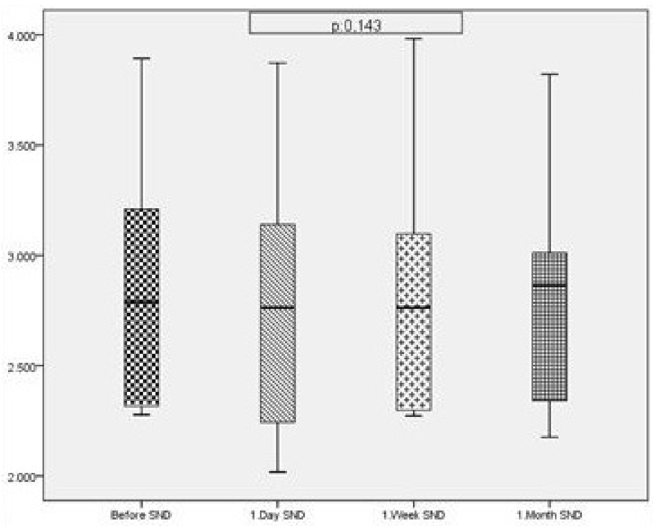

Figure 1: *Subbasal nerve density values of pre-procedure, post- procedure 1st day, post-procedure 1st week, post-procedure 1st month.*

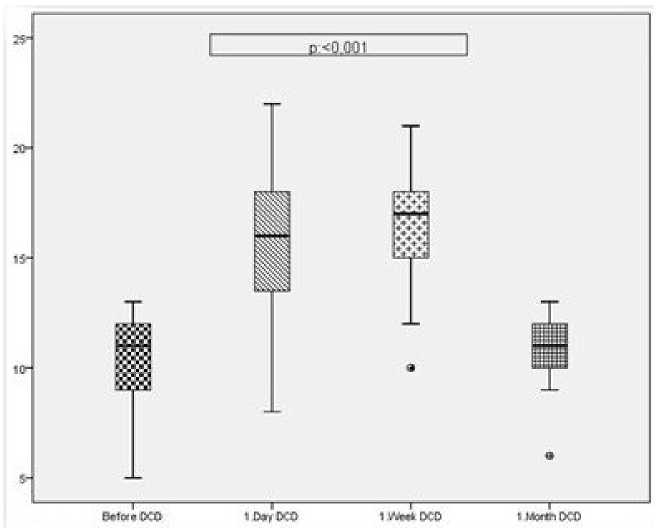

Figure 2: *Dendritic cell density values of pre-procedure, post-procedure 1st day, post-procedure 1st week, post-procedure 1st month*

Table 4: *Correlation between the decrease in IOP intraocular pressure values and dendritic cell dendity changes*

		1st w-baseline IOP	1st m-baseline IOP	1st m- 1st w IOP
1st w-baseline DCD	r p	0,012 0,965		
1st m-baseline DCD	r p		-0,59 0,834	
1st m-1st w DCD	r p			-0,104 0,713

r: correlation coefficient; spearman correlation analyze
DCD: dendritic cell density; w:week; m:month; IOP: intraocular pressure

therapy, may be considered as a safe procedure according to our study results. In addition, the fact that laser trabeculoplasty procedures do not have a negative effect on future trabeculectomy results, may create a rationale for preoperative application of these procedures.[11]

Argon Laser Trabeculoplasty (ALT) is a conventional technique, which creates focal scarring and modification by producing thermal burns in the trabecular meshwork, was first introduced by Wise and Witter in 1979. SLT is an alternative laser trabeculoplasty technique to ALT, which provides similar outcomes without visible thermal damage by using Q switched (3ns) Nd-YAG laser (532 nm), was introduced in 1995.[12-14]

PSLT is a semi-automatic photocoagulation method introduced in 2006, and it reduces thermal damage to the surrounding tissue by providing more shots per area in the trabecular meshwork with a short pulse duration (10-20 ms) and a spot width of 100 µm.[3,4] PSLT uses a special pattern scanning algorithm that ensures full coverage of the trabecular meshwork despite the absence of visible burns.[15] Although the exact mechanism of action of PSLT is not known, the absence of coagulative damage and scarring, similar to SLT, suggests that the reaction is at the cellular level. However, there are some notable differences in PSLT from the treatment parameters of SLT. The treatment duration for PSLT is shorter than SLT; instead of applying ~100 individual laser spots for 360° treatment in SLT, PSLT automatically rotates the aiming beam and delivers multiple laser spots over 32 segments (each segment spans ~11.25°) of the trabecular meshwork for 360° treatment. Consequently, it is hypothesized that PSLT can allow better penetration of TM with less thermal spread.[5,16]

In a recent study, when the patients who underwent SLT and PSLT were compared, it was shown that there was no difference between the two techniques in terms of efficacy and safety as of 6 months, but PSLT was interpreted more comfortably by the patients. This can be explained by the fact that the total treatment time is shorter in PSLT than in SLT.[17] In another study comparing the longer-term cases of ocular hypertension and open-angle glaucoma who underwent SLT and PSLT, no difference was found between the two groups in terms of safety and efficacy.[16] Consistent with previous studies, 36.78% decrease in IOP and mean 0.87 decrease in the need for antiglaucoma agents was achieved at the first month after the PSLT procedure in our study.

The corneal endothelium is a vital structure consisting of a single layer of non-regenerating hexagonal cells and is responsible for the transparency of the cornea by regulating corneal hydration.[18] After laser trabeculoplasty procedures, some alterations can be seen in the corneal endothelium due to both the direct damage of the laser energy and the effect of inflammatory changes.[19] Temporary reduction of corneal endothelium cell count, changes in central corneal thickness, corneal edema, corneal haze, corneal thinning, keratitis, hyperopic shift and topographic changes are some of the alterations which can be possibly seen after SLT.[7,9,20,21] Although the mechanism of the changes is not clear yet, some hypotheses have been emphasized in the literature. It is known that there is an increase in the release of prostaglandins and cytokines to the anterior segment and the formation of free oxygen radicals after SLT.[22] It has been shown that there is a transient increase in lipid peroxide in the aqueous of rabbits treated with SLT. Potential sites of lipid peroxidation via free radical formation include the corneal endothelium and iris, which are rich in polyunsaturated fatty acids.[23] Therefore, the cornea may be one of the areas most affected by inflammatory changes after laser trabeculoplasty.

In an in-vitro study, it was shown that there were similar changes in tight junctions of the corneal endothelium after

SLT and after peroxide exposure, and it was emphasized that endothelial changes after SLT may be associated with inflammation. In the same study, post-SLT endothelial changes were observed widely, not directly in the laser-applied area, suggesting that free oxygen radicals released into the aqueous after SLT might be responsible for these changes.[24] In another study, the fact that endothelial changes were extensive after SLT cases applied to the inferior quadrant supports that endothelial changes were induced by inflammatory agents released into the aqueous.[21]

Corneal nerves have a clear role, both directly and indirectly, in maintaining and improving corneal epithelial integrity and therefore corneal transparency. Subbasal nerve plexus is a structure consisting of unmyelinated nerve fibers running parallel to the cornea between Bowman's layer and basal epithelium, and is currently evaluated quickly, easily and non-invasively by IVCM.[25,26]

Studies with IVCM have shown that SND decreases in inflammatory conditions such as keratoconus, dry eye disease, contact lens wear, neurotrophic keratopathy, corneal dystrophy, vernal and atopic keratoconjunctivitis, and in many systemic diseases. Glaucoma is a chronic condition associated with keratopathy and inflammation, and previous studies have shown a decrease in subbasal nerve density and increased tortuosity in nerves in individuals with glaucoma.[10,25] On the other hand there are studies in the literature showing that there may be no significant change in SND values in cases of dry eye, which is highly associated with inflammation.[27,28] In our study, there was no statistically significant difference between the SND values of pre-procedure, post-procedure 1st day, post-procedure 1st week, post-procedure 1st month. Our study showed that the PSLT procedure, which may also initiate the inflammatory process, has no effect on SND.

Although the healthy cornea is thought to be immunologically privileged; during homeostasis, the presence of resident immature dendritic cells and other resident corneal leukocytes have been clearly demonstrated by many independent researchers. The aforementioned leukocytes can be detected as dendritiform cells in the basal epithelial layer with the help of IVCM. It is known that there is an increase in DCD and size in the presence of inflammation.[10, 27]

Ong et al., with the help of specular microscopy, revealed that dark spots that resorb within about 1 month after SLT.[20] White et al. [21], on the other hand, showed that changes that were not clinically evident or could not be detected by specular microscopy could be revealed by confocal microscopy. In this study, post-SLT dysmorphic cell structures and increased intercellular spaces were analyzed with the help of IVCM. In our study, dendritic cell density, which is known to be highly associated with inflammation, increased after the procedure, but returned to its basal value by the 1st month.

In SLT and PSLT procedures, inflammation underlies both the mechanism of action of the procedures and the basis of complications. The fact that inflammatory changes regressed in about 1 month in our study and previous studies suggests that these changes can be evaluated as an indicator of the effectiveness of the treatment rather than the pathological result.[20,21,24]

In some of the studies conducted with specular microscopy, opinions have been put forward that endothelial cell density and morphology measurements may not reflect the presence of inflammation exactly. In a study, it was detected a temporary decrease in endothelial cell density and central corneal thickness with the help of specular microscopy after SLT in open-angle glaucoma cases, and the reason for this was thought to be edema at the cellular level, which causes an error in the endothelial cell count rather than inflammation. In the same study, it was emphasized that the central corneal thickness decreased despite the decrease in the number of endothelial cells and that this was a result of laser-induced stromal contraction.[7]

On the other hand, there is no contradiction in the literature regarding the accuracy of detecting inflammatory changes, especially dendritic cell density, in demonstrating inflammation with the help of confocal microscopy. Therefore, we think that dendritic cell density will be an objective and powerful method in evaluating inflammation and treatment efficacy after PSLT.

Pseudoexfoliative glaucoma is a specific subtype of open-angle glaucoma that laser trabeculoplasty methods are known to be particularly effective.[29] Since it is well known that PEX material causes progressive corneal endotheliopathy and decrease in endothelial cell density, it can be considered as an independent risk factor for endothelial changes after laser trabeculoplasty.[30] In the study where Wang et al. compared endothelial cell density and morphology, no difference was observed in the PEX group, while Bozkurt et al. revealed that the endothelial cell density was significantly lower in the PEX group.[30,31] In another study, it was shown that endothelial cell density was significantly lower in the PEX group than in the control group, and pleomorphism and polymegatism in endothelial cells in the PEX group were more prominent, especially in cases with high intraocular pressure.[32] On the other hand, there are studies showing that the presence of PEX does not cause additional damage to the corneal endothelium after a single dose of SLT.[33] In our study, no difference was observed between the PEX group and the POAG group in terms of SND and DCD values after a single dose of PSLT.

One of the factors affecting the effectiveness and results of laser trabeculoplasty is the antiglaucomatous drugs used.[17,22] Ocular surface inflammation due to antiglaucomatous eye drop solutions have been reported previously in literature.[34,35] In our study there was a decrease in the mean number of antiglaucomatous drugs used 1 month after PSLT, and this change may possibly have altered the in vivo confocal microscopic findings. In addition considering that especially prostaglandin analogues may contribute to the inflammatory process after LT, the fact that not evaluating the use of these drugs and not discontinuing antiglaucomatous agents before the procedure are limitations of our study. Small sample size of participants, lack of control group and interobserver variability are also another limitations.

In conclusion, in this study, it was observed that there was a significant increase in DND values with the help of IVCM after a single dose of PSLT, but these values decreased to baseline values as of the 1st month.

This is the first study to evaluate DCD and SND values with the help of IVCM after PSLT in open-angle glaucoma and as we know that dendritic cell density has a strong relationship with inflammation, evaluating inflammation by IVCM is the strength of our study. Evaluation of subbasal nerve density and dendritic cell density with IVCM after PSLT may be a biomarker that shows PSLT efficacy as well as the severity of the inflammatory state. Prospective studies with larger samples are needed on this subject.

Declerations:

Competing interest: Author Kaderli declares that he has no conflict of interest. Author Güvenç declares that she has no conflict of interest. Author Şimşek declares that she has no conflict of interest. Author Demirok declares that he has no conflict of interest.

Author Kaya declares that he has no conflict of interest. Author Korkmaz declares that he has no conflict of interest. Author Kaderli declares that she has no conflict of interest. Author Karalezli declares that he has no conflict of interest.

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

Consent to participate: Informed patient consent was obtained from all participants.

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 and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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