



Research Article

Evaluation of the Effect of Plasma Occlusion of Punctum (POP) on Dry Eye Disease Treatment: A 6-month Randomized Clinical Trial

Shima Eghtedari, Farhad Nejat*, Ahang Taghvamanesh

Vision Health research center, Tehran, Iran

*Corresponding author: Farhad Nejat, Vision Health research center, Tehran, Iran

Citation: Nejat F, Eghtedari S, Taghvamanaesh A (2024) Evaluation of the Effect of Plasma Occlusion of Punctum (POP) on Dry Eye Disease Treatment: A 6-month Randomized Clinical Trial. J Med Biomed Discoveries 6: 125. DOI: <https://doi.org/10.29011/2688-8718.100125>

Received Date: 16 May, 2024; **Accepted Date:** 22 May, 2024; **Published Date:** 11 June, 2024

Abstract

Background: The effect of punctum stricture with atmospheric low-temperature plasma has been evaluated in a 6-month randomized clinical study for dry eye disease (DED) treatment. **Methods:** This study included a total of 60 patients with moderate to severe dry eye disease, with the comorbidity of rheumatologic disorders. The control group (CG) with 30 participants continued to receive their previous medical dry eye treatment, and the test group (TG) including 30 patients were treated with plasma occlusion of punctum (POP), as well as their same medical cures. POP method was performed by a surgeon using the PLEXR Plus device over three sessions with a one-week interval. The outcome of this method was proved by visual parameters, OSDI questionnaire, dry eye tests and punctum size measurements. **Results:** As we expected, no specific changes were observed in the uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA) and intraocular pressure of all patients in both groups of this study. Tear meniscus height (TMH), tear break-up time (TBUT) and schirmer tests indicated a significant increase of 79.8%, 69.99% and 86.20%, respectively, in all patients in test group with POP intervention. Additionally, in the TG, Optical coherence tomography (OCT) and slit-lamp examination showed a meaningful reduction in outer punctal diameter, punctal depth, and horizontal inner punctal depth six months after POP procedure (*p-value<0.05). **Conclusion:** It seems that POP procedure with transient stricture of punctum size can be a safe, effective, office-based and low-cost treatment for moderate to severe grade of dry eye disease which is the most prevalent eye disease all over the world.

Keywords: Punctal occlusion, Dry Eye Disease (DED), Plasma technology, Outer punctum diameter, Punctal depth, POP method

Introduction

Dry eye disease (DED) is defined as a multifactorial and common eye disorder that occurs when tear evaporates excessively or is inadequately secreted due to reduced activity of the lacrimal glands [1,2]. In recent studies, the third subtype of DED is associated with decreased wettability, which can be caused by disrupted membrane-associated mucin, especially MUC16. This affects the cornea's ability to remain wet [3,4]. DED is associated with signs and symptoms such as eye discomfort, itching, redness, foreign body sensation, pain, and light sensitivity. In severe cases, it can lead to corneal injury and significantly impact the quality

of life of individuals [5]. However, this condition remains one of the most neglected, with prevalence ranging from 5% to 50% across all age groups and reaching as high as 75% in specific climates [6]. In Iran, our targeted cohort, the prevalence rate ranges from 46.7% to 59 % in some cities [7]. The risk factors for DED can be categorized into two main groups. The first category includes intrinsic factors such as female sex, aging, meibomian gland dysfunction, and rheumatologic disorders. The second category comprises environmental conditions such as certain medication, climate, ocular surgeries, excessive computer usage, and wearing contact lenses [8]. The first line of treating grade 3 and 4 of DED can be the punctal occlusion. The conventional and omnipresent methods include reversible silicon punctum plug, collagen solution (16-week absorbable), thermal cauterization

(total or partial of the punctum), punctal plug suturing, usage of conjunctival flap or graft, destruction (or extirpation) of the canaliculus, and canalicular ligation, and the persistent methods offer benefits to patients suffering from chronic dry eye disease [9-13]. However, in rheumatologic disorders such as Sjögren’s syndrome, rheumatoid arthritis, and lupus, which are believed to have remission and exacerbation periods, it seems that complete occlusion may lead to excessive tearing [14]. Nejat et al. have introduced a novel technique for punctum stricture after one session of PANIS procedure (Plasma assisted noninvasive surgery) by applying one plasma spot on the outer punctum diameter (OPD) [15]. This method is claimed to have a 6-month effect on punctal stricture after three consecutive sessions [16]. In this study, we conducted randomized clinical trial included 60 patients of rheumatologic disorders in control and test group and evaluated the postoperative results of plasma occlusion of punctum (POP), as a new and minimally invasive method in a 6-month period and monitor if the punctum stricture advantages will maintained for six months.

Materials and Methods

Patient selection

Our study was approved by the ethics committee of Semnan

University of Medical Sciences, Semnan, Iran. Informed consent forms were provided to all patients, and after a brief explanation of possible side effects, these consent forms were completed and signed by the patients and collected. The study included 60 eyes of 60 patients referred from the rheumatologic disorders clinic, all diagnosed with definite rheumatologic disorders such as Sjögren’s syndrome, rheumatoid arthritis, along with proof of having grade 3 and 4 of dry eye disease, based on the DEWS grading system (Table 1) [17]. All patients were using commonly prescribed dry eye medications, including artificial tears, lubricant eye gel, and warm compress. The patients were divided into two groups: the control group (CG) consisted of 30 patients with a mean age of 41, comprising 6 males and 24 females, with 24 patients having grade 3 and 6 cases having grade 4 of DED. The test group (TG) consisted of 30 participants (11 males and 19 females) who underwent the POP procedure in addition to their previous medications, with an average age of 48. In the TG, 22 patients had grade 3 and 8 had grade 4 DED. The exclusion criteria are comprised a history of any eye surgeries in the last six months, pregnancy or lactation, acute and chronic eye diseases, participation in other interventional clinical studies concurrently, inability to meet the researchers’ requirements, failure to attend within the specified time frame requested by the researchers, and refusal to sign the informed consent form for study participation.

Dry eye severity	Grade 1	Grade 2	Grade 3	Grade 4
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2
TBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant

Table 1: The DEWS grading system of dry eye disease.

POP procedure for TG

All 30 eyes from 30 patients in TG underwent the POP method. Initially, local anesthesia was administered by applying 3 drops of tetracaine 0.5% (Sina Daro, Tehran, Iran) to the targeted eye at 5-minute intervals for 15 minutes. Subsequently, the POP procedure was performed while the patients were seated behind the slit lamp. One or two plasma spots were applied to punctum using the white handpiece of the PLEXR PLUS device (GMV, srl, Rome, Italy) as a plasma generator (Table 2). One session of this procedure resulted in punctal occlusion for approximately two to five days (supplementary video1). However, we continued to repeat three sessions with a one-week interval for more effective and long-term stricture. One surgeon (F.N.) conducted the POP procedure on all TG patients. Every medication that they were using was continued along with the POP procedures. They came to the Vision Health clinic before and 3 to 6 months after three sessions of their treatment for regular follow-up checkups.

- The device operates using air as the working gas.
- It is powered by a docking station with a voltage of 24 V.
- Handpieces are equipped with an embedded inductive charger with a voltage of 5 V.
- The maximum power output of the device: 2 W.
- The maximum working voltage: 1.3 kVPP.
- The output frequency of the device ranges from 70 to 80 kHz.
- There are three types of handpieces available:
 - White: Peak to peak voltage of 500 V, power of 0.7 W, and frequency of 75 kHz.
 - Green: Peak to peak voltage of 600 V, power of 1 W, and frequency of 75 kHz.
 - Red: Peak to peak voltage of 700 V, power of 2 W, and frequency of 75 kHz.
- The device can absorb a maximum power of 120 W.
- It employs a sterile disposable needle made of stainless steel as the applicator electrode.
- The device is classified as IIb, indicating a medium-high risk level.

*Note: The white handpiece was used for this study.

Table 2: The PLEXR PLUS device characteristics.

Protocol for CG

All 30 participants who met the inclusion criteria of our study will continue their medical treatments, which include artificial tear three times a day (TDS), lubricant eye gel at bedtime (HS), and warm compress once a day, whereas they refuse to have punctal occlusion with punctum plug. Additionally, every participant should visit the Vision Health clinic before and six months after initial step of our study, for checkup tests. Our team ensures that every individual uses their medications correctly and regularly.

Measurement of Parameters

In this study, the effectiveness of the POP method was investigated through a series of ophthalmic examinations. These assessments involved 12 parameters, conducted before and 3 to 6 months after 3 consecutive sessions of POP. The parameters included uncorrected

distance visual acuity (UCVA), best-corrected distance visual acuity (BCVA), ocular surface disease index (OSDI), intraocular pressure (IOP) measured by a rebound tonometer (iCare Finland Oy, Vantaa, Finland), punctal depth (PD) and outer punctal diameter (OPD) [18] with anterior Segment Optical Coherence Tomography, (AS-OCT, Topcon DRI OCT Triton, Japan). In order to capture an image of the punctum using the OCT device, it is necessary to carefully and gently rotate the lower edge of the inferior eyelid outwards using the applicator with minimal pressure, thereby avoiding any changes to the structure and depth of the displayed punctum, or at least minimizing any changes. After capturing the image, the punctal depth (PD) and outer punctal diameter (OPD) are determined using the OCT device software. Based on the observed image (Figure 1), OPD refers to the distance between the highest points of the two curved edges of the punctum, while the PD is defined as a linear measurement from the deepest part observed of the punctum, parallel to the axis of the image frame, to the OPD line. The outer punctal diameter vertically (OPDV), outer punctal diameter horizontally (OPDH), and inner punctal diameter horizontally (IPDH) were measured using the CSO slit-lamp, as shown in Figure 2. Dry eye tests such as tear meniscus height (TMH) and tear break-up time (TBUT) were evaluated by an ocular surface portable analyser (OSA-VET, SBM Sistemi, Torino, Italy), while the Schirmer test was conducted using Schirmer strips (ERC Sagulik, Ankara, Turkey). All parameters were obtained by one expert technician. The study design was blinded for the technician, without knowing which patients belonged to which group. The 12-item OSDI questionnaire will be used to measure symptoms of dry eye from the participant's perspective. The OSDI questionnaire includes three subcategories: OSDI-symptoms, which mention ocular discomfort such as painful eyes; OSDI-function, which mentions limitations in daily performance such as reading and working on a computer; and the third subgroup, OSDI-triggers, which mentions environmental triggers such as wind. OSDI scores can range from 0 to 100, that higher scores indicating more symptoms and a more severe grade of dry eye disease. [19]. Last but not least, the satisfaction factor contains 2 questions that TG participants should answer during the last session of their visit to our clinic. The questions are as follows:

1. Would you prefer to use the POP method for your other eye treatment?
2. If any of your family members have the same condition as you, would you introduce the POP method to them?

The answers to these questions are ranged from 0 to 10, where 0 indicates maximum dissatisfaction and negative feelings about the POP procedure, and 10 indicates maximum satisfaction and positive feelings about this novel technique.

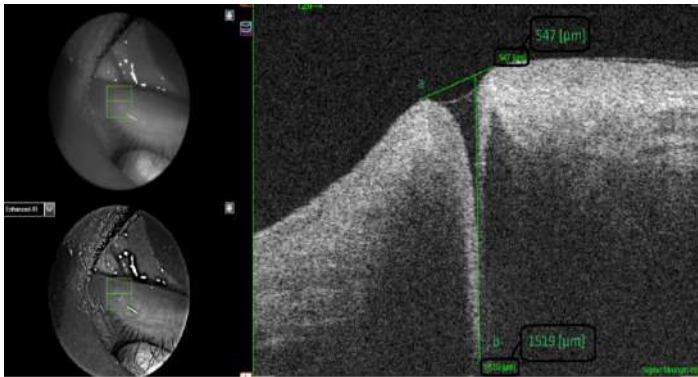


Figure 1: AS-OCT imaging of punctum a: OPD, Outer Punctal Diameter. b: PD: Punctal Depth

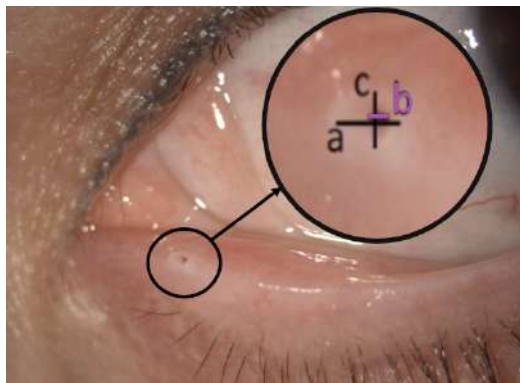


Figure 2: a: OPDH, Outer Punctal Diameter Horizontal, b: IPDH: Inner Punctal Diameter Horizontal, c: OPDV, Outer Punctal Diameter Vertical

Statistical Analysis

The results are presented as means \pm standard deviations and ranges. The pre- and postoperative values of parameters in the

control group (CG) are represented by P-value1, while those in the test group (TG) are represented by P-value2. The postoperative values of all parameters in the TG compared to CG are represented by *P-value and were statistically analyzed using Student's paired t-test. A P-value < 0.05 was considered statistically significant.

Results

Sixty eyes from sixty patients included in this randomized clinical trial. Thirty patients in TG undergoing POP intervention and 30 patients of CG continue with their previous medication. Patient's characteristics are mentioned in table 3. According to the extracted results, UCVA, BCVA and IOP remained expectedly unchanged in both groups, which shows that the POP method has no side effects on vision and ocular health (Supplementary table 1, Supplementary table 2).

In the Control group (CG), there are 30 patients, with 24 patients diagnosed with grade 3 and 6 cases with grade 4 of dry eye severity. Among these, 1 patient decreased from grade 3 to grade 2, and 28 cases remained on grade 3. As shown in Table 3, there were no significant changes in any of the measured parameters in the control group. The Schirmer test and TBUT increased by 1.55% (P-value1=0.73) and 1.67% (P-value1=0.71), respectively, but TMH decreased by 2.31% (P-value1=0.55) after an average of 4.33 ± 1.12 months post-examination (Table 3). No significant changes in punctum sizes were observed in the CG, either by OCT or slit-lamp imaging (Figure 4-D and Figure 5-D). The presence of minor changes in punctal sizes in the control group may be caused by differences in individual's eye characteristics, environmental conditions, and human errors. It is worth noting that OCT-PD and OCT-OPD increased by 0.68% (P-value1=0.57) and 0.91% (P-value1=0.31) respectively, while IPD-horizontal increased by 2.11% (P-value1=0.43). OPD-vertical and OPD-horizontal decreased by 1.43% (P-value1=0.15) and 1.35% (P-value1=0.11) respectively. In CG the mean difference for OSDI questionnaire is 17.8.

Case	UCVA		BCVA		IOP		OSDI		Case	UCVA		BCVA		IOP		OSDI	
	Before	After	Before	After	Before	After	Before	After		Before	After	Before	After	Before	After	Before	After
P1	7/10	7/10	10/10	10/10	14	14	78.9	69.2	P16	8/10	8/10	10/10	10/10	13	13	94.8	62.1
P2	7/10-	7/10-	10/10	10/10	13	13	84.3	62.3	P17	9/10-	9/10-	10/10-	10/10-	12	12	96.7	69.3
P3	7/10	7/10	8/10	8/10	12	12	98.2	65.5	P18	8/10	8/10	9/10	9/10	14	14	99.2	74.1
P4	8/10	8/10	9/10	9/10	12	12	92.9	67.3	P19	10/10	10/10	10/10	10/10	17	17	89.3	77.3
P5	7/10	7/10	10/10-	10/10-	14	14	89.3	65.9	P20	10/10	10/10	10/10	10/10	16	16	86.5	76.3
P6	6/10	6/10	10/10	10/10	12	12	87.8	64.7	P21	10/10	10/10	10/10	10/10	15	15	87.3	78.2
P7	10/10	10/10	10/10	10/10	16	16	88.5	82.5	P22	10/10	10/10	10/10	10/10	12	12	92.3	77.5
P8	10/10	10/10	10/10	10/10	15	15	89.8	73.2	P23	7/10	7/10	10/10	10/10	19	19	88.6	74.2
P9	10/10	10/10	10/10	10/10	19	19	68.5	65.5	P24	6/10	6/10	10/10	10/10	21	21	97.3	89.3
P10	10/10	10/10	10/10	10/10	19	19	97.3	72.3	P25	10/10	10/10	10/10	10/10	19	19	84.2	69.2
P11	9/10	9/10	10/10	10/10	16	16	94.6	54.8	P26	10/10	10/10	10/10	10/10	12	12	89.2	68.5
P12	8/10	8/10	10/10	10/10	16	16	84.7	68.9	P27	10/10	10/10	10/10	10/10	16	16	82.3	79.3
P13	10/10	10/10	10/10	10/10	12	12	85.6	66.3	P28	10/10	10/10	10/10	10/10	19	19	67.5	64.3
P14	10/10	10/10	10/10	10/10	11	11	87.4	74.9	P29	10/10	10/10	10/10	10/10	20	20	78.3	73.6
P15	8/10	8/10	10/10	10/10	13	13	88.5	67.5	P30	10/10	10/10	10/10	10/10	21	21	69.4	65.3

Supplementary Table 1: Visual parameters, Intraocular pressure (IOP) and Ocular surface disease index (OSDI) of Control group (CG)

In the Test group (TG), twenty-two patients with grade 3 and eight cases with grade 4 preoperatively underwent the POP procedure with a mean follow-up period of 4.42 ± 1.10 months. Fourteen patients were completely cured, eight cases became grade 1, six cases grade 2, and two cases grade 3. The Schirmer test revealed an 85% increase ($P\text{-value} < 0.05$) in all participants, while TBUT and TMH significantly improved by about 55% ($P\text{-value} < 0.05$) and 79% ($P\text{-value} < 0.05$) postoperatively (Table 3). The measurements obtained during the mean 4.42 ± 1.10 months postoperative period, showed a significant decrease in punctum size as assessed by AS-OCT. Specifically, there was a 19% decrease in PD ($P\text{-value} < 0.05$)

and a 22% decrease in OPD ($P\text{-value} < 0.05$) (Figure 3) (Figure 4, A-C). Additionally, measurements of OPD-Vertical, OPD-Horizontal and IPD-Horizontal obtained by slit lamp (Figure 5, A-C) revealed a 27% ($P\text{-value} < 0.05$), 31% ($P\text{-value} < 0.05$), and 36% ($P\text{-value} < 0.05$) decrease, respectively. These findings indicate a significant stricture of the punctum persisting for approximately 3 to 6 months after the POP procedure. In TG patients, the mean difference value of the OSDI questionnaire is 53.34, which is one of the encouraging factors to continue this novel technique as a complement to medical treatment in moderate and severe dry eye disease.

Case	UCVA		BCVA		IOP		OSDI		Case	UCVA		BCVA		IOP		OSDI	
	Before	After	Before	After	Before	After	Before	After		Before	After	Before	After	Before	After	Before	After
P1	4/10	4/10	4/10	5/10	4/10	4/10	96.2	32.5	P16	8/10	8/10	10/10	10/10	13	13	79.8	0
P2	10/10-	10/10-	10/10	10/10	10/10-	10/10-	79.4	14.7	P17	9/10-	9/10-	10/10-	10/10-	12	12	73.5	5.9
P3	4/10	4/10	4/10	5/10+	4/10	4/10	75.6	17.2	P18	8/10	8/10	9/10	9/10	14	14	78.4	7.9
P4	10/10-	10/10-	10/10	10/10	10/10-	10/10-	94.9	29.3	P19	10/10	10/10	10/10	10/10	17	17	69.2	2.1
P5	9/10-	9/10-	9/10	9/10	9/10-	9/10-	93.6	6.2	P20	10/10	10/10	10/10	10/10	16	16	98.3	3.5
P6	10/10	10/10	10/10	10/10	10/10	10/10	84.1	7.5	P21	10/10	10/10	10/10	10/10	15	15	59.9	19.3
P7	10/10	10/10	10/10	10/10	10/10	10/10	87.3	39.4	P22	10/10	10/10	10/10	10/10	12	12	57.3	6.8
P8	9/10	9/10	10/10	10/10	9/10	9/10	96.2	47.2	P23	7/10	7/10	10/10	10/10	19	19	39.2	29.2
P9	2/10-	2/10-	10/10	10/10	2/10-	2/10-	67.5	3.4	P24	6/10	6/10	10/10	10/10	21	21	85.2	7.5
P10	7/10	7/10	7/10+	7/10+	7/10	7/10	96.8	21.3	P25	10/10	10/10	10/10	10/10	19	19	86.9	6.3
P11	10/10-	10/10-	10/10	10/10	10/10-	10/10-	74.3	7.8	P26	10/10	10/10	10/10	10/10	12	12	88.2	0
P12	9/10-	9/10-	10/10	10/10	9/10-	9/10-	79.8	9.9	P27	10/10	10/10	10/10	10/10	16	16	67.9	0
P13	10/10-	10/10-	10/10	10/10	10/10-	10/10-	84.5	4.5	P28	10/10	10/10	10/10	10/10	19	19	84.2	3.9
P14	10/10	10/10	10/10	10/10	10/10	10/10	73.6	15.9	P29	10/10	10/10	10/10	10/10	20	20	72.9	0
P15	10/10	10/10	10/10	10/10	10/10	10/10	79.2	0	P30	10/10	10/10	10/10	10/10	21	21	83.7	0

Supplementary Table 2: Visual parameters, Intraocular pressure (IOP) and Ocular surface disease index (OSDI) of Test group (TG).

Along all steps of the procedure and postoperative follow-ups, no patient complained about eye redness, foreign body sensation, epiphora and other dry eye symptoms. All participants in TG have been reported no complaint except a topical mild pain during or in some cases a few hours after POP procedure. We have not observed any complication during and in postoperative follow-up period.

	CG: Before	CG: After 3-6 months	P-value 1	TG: Before	TG: After 3-6 months	P-value 2	*P-value
OPD (μm) Mean±SD (OCT)	478±128	483±123	0.31	551±114	447±112	<0.05	0.26
PD (μm) Mean±SD (OCT)	1022±348	1029±341	0.57	1207±374	938±365	<0.05	0.33
Slit-lamp OPDH (μm) mean±SD	764±165	753±149	0.11	840±190	608±138	<0.05	<0.001
Slit-lamp IPDH (μm) mean±SD	236±72	241±60	0.43	280±99	185±56	<0.05	<0.001
Slit-lamp OPDV (μm) mean±SD	737±209	727±194	0.15	748±171	563±134	<0.05	<0.001

TMH (μm) mean \pm SD	0.173 \pm 0.04	0.177 \pm 0.03	0.55	0.13 \pm 0.04	0.23 \pm 0.04	<0.05	<0.001
TBUT(s) mean \pm SD	6 \pm 1.87	6.1 \pm 1.49	0.71	5 \pm 1.57	8.42 \pm 2.24	<0.05	<0.001
Schirmer test (mm) in 5m mean \pm SD	10.96 \pm 2.12	11.13 \pm 2.63	0.73	8.80 \pm 1.93	16.42 \pm 2.13	<0.05	<0.001

P-value 1 calculates significant differences of the pre and post examinations in CG.

P-value 2 calculates significant differences of the pre and post operation in TG.

*P-value calculates the post-op significant differences of control group and test group.

Table 3: Preoperative and postoperative comparison of parameters in control group and test groups and the statistical analyzing numbers.

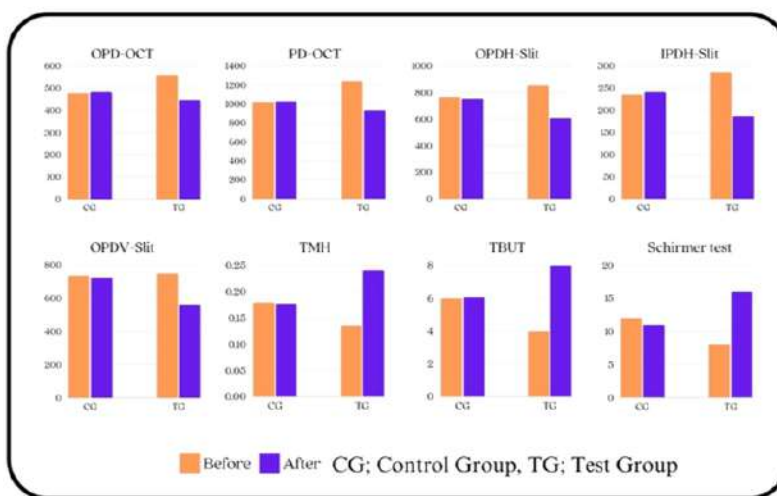


Figure 3: The difference of parameters in control group (CG) and test group (TG), before and after six-months.

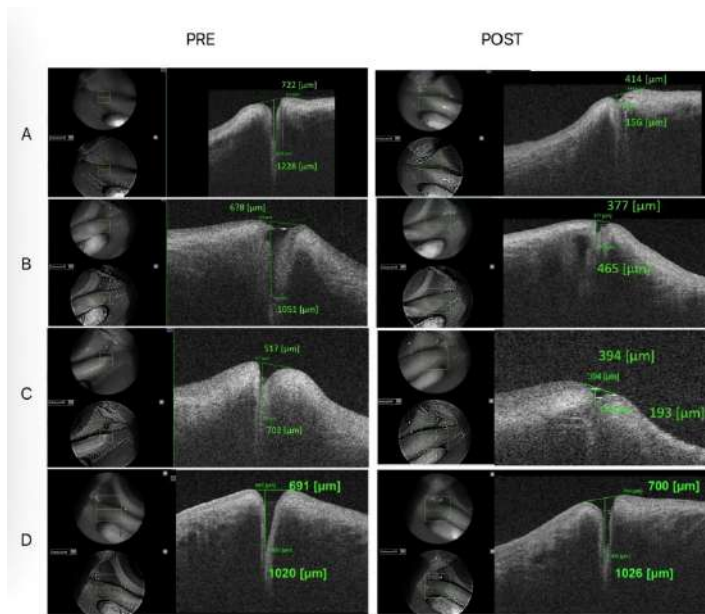


Figure 4: OCT imaging of punctum. A-C) Examples of before and after of TG, D) Example of before and after of CG.

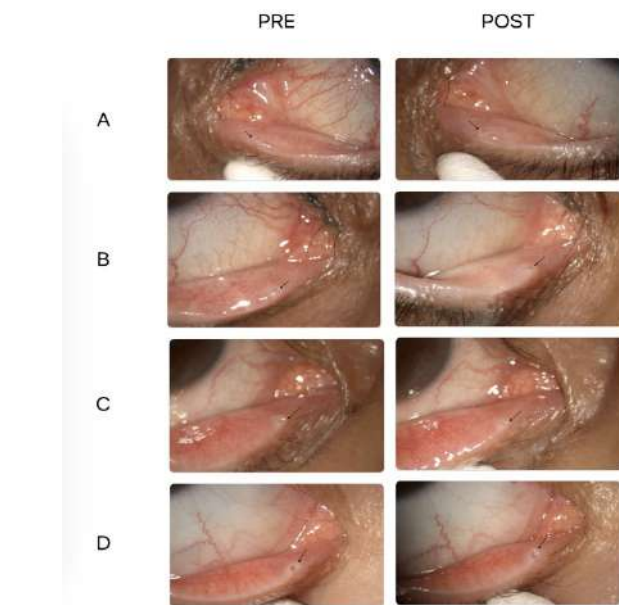


Figure 5: slit lamp imaging of punctum A -C) Examples of Before and After of TG, D) Example of Before and After of CG.

Discussion

Dry eye disease (DED) is one of the most challenging common eye disorders. It occurs when the natural tears of patients are disrupted in quality and quantity, leading to insufficient wetting of the ocular

surface. This can result in symptoms such as redness, foreign body sensation, itching, burning, eye fatigue, photophobia, and corneal epitheliopathy [20]. Considering the relationship between DED and tear film instability, hyperosmolarity, and inflammation of the ocular surface, practical treatment modalities mainly include lubricant tears, ointments and for reduction of inflammatory, FDA approved drugs such as Lifitegrast (Xiidra) and Cyclosporine 0.09% (Cequa) may help [21]. In severe cases where medication is inadequate, interventional procedures such as punctal occlusion may be helpful in retaining natural tears on the ocular surface for longer periods [22].

The conventional methods for punctal occlusion are thermal Cauterization, Radiofrequency Electrosurgery, Combined Canalicular Cauterization and Punctal Suturing, Punctal Plugs and Punctal Occlusion with Amniotic Membrane [8, 23-26]. In all fields of medicine, the preferred initial treatment option is typically the least invasive approach. Surgical techniques, while being effective, carry potential drawbacks because of tissue damage, permanence, infection risk, and the need for an operating room. These interventions are typically reserved for severe cases of DED to prevent reopening of the puncta. However, they may lead to epiphora in patients with rheumatologic diseases, which can have periods of remission and exacerbation. During remission, patients may experience nearly normal lacrimal gland secretion, and if tears cannot drain properly, patients may suffer from tearing.

Ervin et al. have published their findings in a Cochrane database after reviewing 18 trials that contain 1249 eyes from Austria, Canada, China, Greece, Japan, Mexico, Netherlands, Turkey, the UK, and the USA. They claimed that, in spite of effective reported results in these articles for punctal plugs, they unmask the inconclusiveness of this DED treatment [8]. Woo Park et al. reported that high-frequency radio-wave electro-punctal occlusion on 79 eyes at Samsung Hospital is a promising treatment for aqueous-deficient dry eye disease (DED) [23].

In recent studies, Nejat team initiate a novel technique for constricting punctal depth and outer punctal diameter concurrent in a single session and 3 consecutive sessions with office-based PANIS treatment instead of complete occluding with heat or radiofrequency waves and published them in two different studies [15, 16]. Of course, these studies were conducted after safety evaluations in the animal phase, wherein plasma spots were applied to rabbit eyes. The rabbits were followed for 6 months after exposure, and histopathological tests conducted after 1 month and 6 months showed no persistent or deep effects of plasma application on the conjunctiva. [27, 28]. In another research, Inflammatory cytokines in tear and serum has checked 4 times within 6 months follow-up after plasma spots on Rats conjunctiva, and this study also reported no persistent inflammatory responses [29]. After 3 animal studies, human ocular surface diseases have

been targeted to treating with atmospheric low-temperature plasma and published case series studies, including conjunctivochalasis, conjunctival cyst, pinguecula, pterygium, punctal occlusion, conjunctival concretion, pseudophakic bullous keratopathy, conjunctival nevus [15, 30-34]. All these novel modalities have been taught to ophthalmologists all over the world, as a safe, office-based and effective approaches [35]. The plasma generator that defined for ophthalmic diseases generate plasma spots with ionizing the air between the tip of the device and the target tissue, thus this plasma will cause sublimation spot by spot on the aimed pathology on eye.

In the present study, Nejat et al. utilized the POP technique for punctal stricture, aiming not only to enhance tear preservation on the ocular surface but also to prevent epiphora and associated complications from surgical punctal occlusion. This new study, features more precise measurements of punctum's before and after stricture with POP, encompassing five different parameters and a larger number of patients in the test group and the control group. The observed improvement in the test group, correlated with puncta stricture that is absent in the control group, emphasizes the method's efficacy in treating DED. This approach proves effective, simple, safe, cost-effective, and reversible, particularly beneficial for rheumatoid patients with treatment challenges. However, the study faces limitations, including potential human errors in OCT imaging measurement due to variations in eyelid everting and operator expertise. Moreover, a larger sample size and longer follow-up period would be necessary for more definitive claims about the POP technique and its possible side effects.

Conclusions

It appears that the POP method offers a safe, effective, and cost-efficient approach to punctal stricture for treating dry eye disease, notably by enhancing tear preservation on the ocular surface. This is particularly relevant for rheumatologic patients with uncertain lacrimal gland secretion, as stricture of the tear drainage system serves as a preferable alternative to complete occlusion. POP may serve as an office-based alternative to invasive and irreversible modalities for managing moderate to severe dry eye disease.

Author Contributions: F.N. Conceptualization and methodology and supervision, Sh.E. Data curation and writing (review and editing) and visualization and project administration, A.T. writing (original draft) and formal analysis. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Erin C O'Neil, Matthew Henderson, Mina Massaro-Giordano, Vatinee

- Y Bunya (2019) Advances in dry eye disease treatment. *Curr Opin Ophthalmol* 30(3): 166-178.
2. Tsubota K, Yokoi N, Shimajaki J, Watanabe H, Dogru M, et al. (2017) New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. *The ocular surface* 15(1): 65-76.
 3. Yokoi N, GA Georgiev (2018) Tear film-oriented diagnosis and tear film-oriented therapy for dry eye based on tear film dynamics. *Investigative Ophthalmology & Visual Science* 59(14): DES13-DES22.
 4. Kato H, Yokoi N, Watanabe A, Komuro A, Sonomura Y, et al. (2024) Effect of Punctal Occlusion on Blinks in Eyes with Severe Aqueous Deficient Dry Eye. *Diagnostics* 14(1): 3.
 5. Sharma S, Donthineni PR, Iyer G, Chodosh J, De la Paz MF, et al. (2023) Keratoprosthesis in dry eye disease. *Indian Journal of Ophthalmology* 71(4): 1154-1166.
 6. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanonot K, et al. (2017) TFOS dews ii epidemiology report. *The ocular surface* 15(3): 334-365.
 7. Aghaie H (2023) Dry Eye in Iran. *Archives of Persian Ophthalmology* 4: 216-228.
 8. Ervin AM, A Law, AD Pucker (2017) Punctal occlusion for dry eye syndrome. *Cochrane Database Syst Rev* 6(6).
 9. Singh R, Yung A, Coco G, Sinha S, Dohlman TH, et al. (2020) Efficacy and retention of silicone punctal plugs for treatment of dry eye in patients with and without ocular graft-versus-host-disease. *The ocular surface* 18(4): 731-735.
 10. Jehangir N, Bever G, Mahmood SMJ, Moshirfar M (2016) Comprehensive review of the literature on existing punctal plugs for the management of dry eye disease. *Journal of ophthalmology* 9312340.
 11. Xu X, Awwad S, Gomex LD, Lorenzo CA, Brocshini S, et al. (2021) 3D Printed Punctal Plugs for Controlled Ocular Drug Delivery. *Pharmaceutics* 13(9): 1421.
 12. Liu D, Y Sadhan (2002) Surgical punctal occlusion: a prospective study. *British journal of ophthalmology* 86(9): 1031-1034.
 13. Anitha V, R Meenakshi, M Vanathi (2021) Update on Surgical Interventions in Management Of Dry Eyes. *Delhi Journal of Ophthalmology* 31(4): 9-18.
 14. Abd-Allah NM, Hassan AA, Omar G, Hamdy M, Abdelaziz ST, et al. (2020) Dry eye in rheumatoid arthritis: relation to disease activity. *Immunological Medicine* 43(2): 92-97.
 15. Nejat F, Jadidi K, Eghtedari S, Nabavi NS (2021) Evaluation of efficacy of plasma assisted non-invasive surgery (PANIS) as a novel approach for temporary punctal occlusion: a clinical case series. *SCIREA Journal of Clinical Medicine* 6(6): 421-432.
 16. Nejat F (2022) Case Series Study.
 17. MichaelA Lemp M (2007) The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop (2007). *Ocul Sur* 5(2): 75-92.
 18. Sung Y, JS Park, H Lew (2017) Measurement of lacrimal punctum using spectralis domain anterior optical coherence tomography. *Acta Ophthalmol* 95(7): e619-e624.
 19. Vitale S, Goodman LA, Reed GF, Smith JA (2004) Comparison of the NEI-VFQ and OSDI questionnaires in patients with Sjögren's syndrome-related dry eye. *Health Qual Life Outcomes* 2: 1-11.
 20. Al-Mohtaseb Z, Schachter S, Shen BL, Garlich J, Trattler W (2021) The relationship between dry eye disease and digital screen use. *Clin Ophthalmol* 15: 3811-3820.

21. Sheppard JD, Torkildsen GL, Lonsdale JD, Ambrosio FAD, McLaurin EB, et al. (2014) Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. *Ophthalmology* 121(2): 475-483.
22. Craig JP, Nicols KK, Akpek Ek, Cafferey B, Dua HS, et al. (2017) TFOS DEWS II definition and classification report. *The ocular surface* 15(3): 276-283.
23. Park JW, Han J, Choi Wk, Kim J, Choi CY (2023) Simple surgical punctal occlusion with high frequency radiowave electro-surgery. *BMC Ophthalmol* 23(1): 49.
24. Kuroda K, Toshida H, Sorita Y, Ichikawa K, Matsuzaki Y, et al. (2023) Surgical punctal occlusion; combined lacrimal canaliculi cauterization and punctal suturing for severe dry eye. *J Ophthalmic Vis Res* 18(2): 143-149.
25. Nagai N, H Otake (2022) Novel drug delivery systems for the management of dry eye. *Adv Drug Deliv Rev* 191: 114582.
26. Wong JC, A Barak (2024) Managing Dry Eye Disease with Novel Medications: Mechanism, Study Validity, Safety, Efficacy, and Practical Application. *Pharmacy* 12(1): 19.
27. Nejat F, Jadidi K, Amoli FA, Bagheri S, Aghamollaei H, et al. (2021) Safety evaluation of the atmospheric low-temperature plasma (ALTP) on the conjunctiva: an animal study and histopathological findings; 6-month follow-up. *BMC ophthalmology*, 2021. 21(1): 333.
28. Nejat F, Nabavi NS, Nejat MA, Aghamollaei H, Jadidi K (2019) Safety evaluation of the plasma on ocular surface tissue: an animal study and histopathological findings. *Clinical Plasma Medicine* 14: 100084.
29. Nejat F, Aghamollaei H, Jadidi K, Nejat MA, Nabavi NS, et al. (2021) The assessment of the concentration of candidate cytokines in response to conjunctival-exposure of atmospheric low-temperature plasma in an animal model. *BMC ophthalmology* 21(1): 417.
30. Nejat F, Nabavi NS, Nejat MA, Jadidi K, Eghtedari S (2021) A Novel Approach to Treatment of Pinguecula Using Atmospheric Low-temperature Plasma: A Clinical Case Series. *American Journal of Clinical and Experimental Medicine* 9(5): 148-152.
31. Nejat F, Nabavi NS, Moradi M, Jadidi K, Eghtedari S (2021) Evaluation of Plasma-Assisted Noninvasive Surgery (PANIS) As a New Approach for Pterygium Removal with Amniotic Membrane Transplantation (AMT); a Clinical Case Series. *International Journal of Innovative Research in Medical Science* 6(11): 808-813.
32. Nejat F, Jadidi K, Eghtedari S, Nabavi NS, Bagheri S, et al. (2022) Evaluating plasma assisted noninvasive surgery (PANIS) as a new method for pterygium removal; a clinical case series. *J Clin Images Med Case Rep* 3(4): 1782.
33. Nejat F, Jadidi K, Eghtedari S, Nabavi NS (2023) Sublimation of Benign Conjunctival Nevi Using Plasma-Assisted Noninvasive Surgery: A Clinical Case Series. *Iranian Journal of Medical Sciences* 48(1): 85-90.
34. Nejat F, Eghtedari S (2023) Plasma technology instead of suture and glue in pterygium removal surgery with conjunctival rotational flap; A 1 year follow up Case report. *Medical Research Archives* 11(2).
35. Eghtedari S, Nejat F, Jadidi K, Nabavi NS (2022) Ophthalmology Webinars Have the Potential to Enhance the Knowledge of the Participants and Change their Attitude About PANIS Method. *Int J Ophthalmol Clin Res* 9(3): 139.