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Evaluation of efficacy of plasma assisted noninvasive surgery (PANIS) as a novel approach for temporary punctal occlusion: a clinical case series

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Abstract

Background: Several studies have reported plasma-assisted noninvasive surgery (PANIS method) as a simple, inexpensive, office-based, minimally invasive, effective technique for treating some ocular surface diseases. This study aims to explore the efficacy of this method for occluding tear drainage system, temporary, in order to treat dry eye disease.

Methods: Study was undertaken in six patients with moderate to severe dry eye (Schirmer's test < 10 mm and TBUT < 10 sec). The inferior puncta were fused using white handpiece of the plasma generator device (Plexr, GMV s.r.l Grottaferrata, Italy) under topical anesthesia and they remained occlude for 2-5 days. The efficacy of the PANIS method was assessed with comprising Refraction, visual acuity, intraocular pressure (IOP), corneal fluorescein staining score (CFS), contrast sensitivity (CS), Schirmer test values, dry eye tests, and ocular surface disease index (OSDI) questionnaire which were collected before, 1week, 1month and 6 months after the procedure and during the first week after this treatment, the slit-lamp examination was performed every day.

Results: All patients showed a significant decrease in corneal fluorescein staining score (CFS) and OSDI questionnaire. In the first three days after procedure, tear meniscus height and tear beak-up time had remarkably improved. Moreover, daily slit-lamp examinations during the first week showed that puncta remained occlude for 2-5 days. In addition, refraction, visual acuity and intraocular pressure showed no considerable change during the 6-month follow-up.

Conclusion: According to the findings**,** the PANIS method seems to be a temporary effective approach for treating dry eye disease (DED). Since no Signs and symptoms of DED were observed within the first week, this novel technique was concluded to be able of evaluating pre-permanent punctual occlusion and also first week after procedure would make a good time for repairing damaged ocular surface with any particular reasons.

Keywords: Temporary punctal occlusion; Plasma; Dry eye disease; Ocular surface disease

1. Introduction

Punctal occlusion is accomplished to treat dry eye disease(DED) by retaining tear on the ocular surface [1].This mechanical occluding can be exerted temporarily or permanently, compatible with patient's condition and depending on the severity of dryness [2, 3]. DED is described as a multifactorial disorder of the tearing system and ocular surface which is categorized into two primary types contain, tear evaporation due to meibomian gland dysfunction and insufficient tear production that leads to aqueous deficiency [4-7]. Since in the tear instability situation, the protective qualities that are necessary for eye's structure and function, are not maintain on the eye's surface, , damage to the ocular surface represent by [8] complaints such as redness, foreign body sensation, ocular fatigue, pain, itching, irritation and visual acuity alternation [9].The generally Prevalence of DED ranges from 5-34% [10]. For example, in the United States it's prevalence is 7% and in Taiwan and Japan is 33% [11-13]. Sequel to this, DED is one of the most common reasons for visiting an ophthalmologist. Multifactorial mechanisms can cause dry eye disease, such as advanced age [14], female sex, smoking, extreme heat or cold weather conditions, low relative humidity [15], long use of video displays [16-18], refractive surgery [19], rheumatoid arthritis [20], contact lens wear and certain medications [21]. The first step to be emancipated from dry eye is changing lifestyle .Avoiding long exposure to screens, increasing atmosphere humidity, enhance

omega-3 in daily diet [22] and not directly placing in front of air conditioners or hair dryers [23, 24] are the most helpful methods to be followed in your daily life. Medical management tips for DED usually include artificial tears [25], ointments, topical cyclosporine [26] and topical corticosteroids [27]. In some cases with corneal epithelial defect, autologous serum is the most effective anti-inflammatory medication. In cases that it is necessary to turn into non-pharmacologic therapies, punctal occlusion is suggested as a surgical therapy to prevent draining tear from the ocular surface [28, 29].

In recent years, the plasma phenomenon -as the fourth state of matter- has been widely utilized in medicine for activating, controlling and catalyzing reactions and complex biochemical procedures. Plasma reactive components have the potential of being applied for various therapeutic purposes in living tissues [30]. For instance wound healing, blood coagulation[31], sterilization, tissue regeneration in dermatologic field [32] and even cancer therapy [30, 32-34]. Plasma-assisted noninvasive surgery (PANIS) has been developed and used in the ophthalmic field by Nejat et al. for the first time. In this therapeutic method, the atmospheric pressure low- temperature plasma (ALTP) [35] is used to treat ocular surface disorders such as conjunctival cyst [36] and conjunctivochalasis [37] and doubtless they had already assessed the safety of this method in animal models using histopathological examinations and cytokine factors assessments [38]. In the present study, the clinical efficacy of this inexpensive and simple method has been evaluated, for temporary punctal occlusion in order to treat DED.

2. Materials and Methods:

2.1. Study design

Over six-months, a case series study, conducted from 2019 to 2020 in Vision Health research center, Tehran, Iran, in adherence to the tenets of the Declaration of Helsinki. In addition to providing written informed consent from every participant, the research was registered in the ethics committee of Semnan University of Medical Sciences, Semnan, Iran. (Identifier IR.SEMUMS.REC.1398.319)

2.2. Inclusion criteria

The impulsion of temporary punctal occlusion defines as two reasons. Foremost cause is to deliberate occluding, in short term condition to decide for permanent block. Many patients

may be diagnosed to be involved in moderate to severe dry eye disease, but not all of them necessarily need surgical permanent punctal occlusion owing to post operation symptoms like, epiphora. Second justification is that, sometimes patients *per se* are in temporary situation. Obviously, after specific surgeries (DSEAK, PK, refractive surgeries and etc.) ocular surface go through special circumstances that might require more natural tear in that area for a while, temporary punctal occlusion can be the best choice in this cases. Six eyes of six patients (mean age 56 years old, 5 left eye and 1 right eye), with moderate to severe dry eye disease, met the inclusion criteria and choose for temporary obstruction of inferior puncta. Patient's Grades of DED were determined based on Delphi Panel dry eye severity grading scheme.

2.3. Surgical technique

Patients were asked to be placed behind the slit-lamp, after being anesthetized with 3 drops of 0.5% topical tetracaine (Sina Darou, Tehran, Iran) with 5 min intervals .This novel technique is to apply 1 or 2 spots on puncta for occluding them(Figure 1). For this aim, surgeon may use white headpiece of plexr device (GMV s.r.l, Grottaferrata, Italy) (Table 1). One surgeon did all occluding procedure (Supplementary video 1). It should be noted that depending on the grade of dryness, ophthalmologist could decide on occluding inferior or superior or both drainage systems. After 2 to 5 days puncta was reopened. Patients received Artelac eye drop (Bausch + Lomb, Laval, Quebec, Canada) every 6 hours for 1 week and Liposic eye gel (Bausch + Lomb, Laval, Quebec, Canada) at bedtime for 1 month, as the postoperative medications.

Figure 1. (a) Preoperative (b) Postoperative - 1 week after procedure

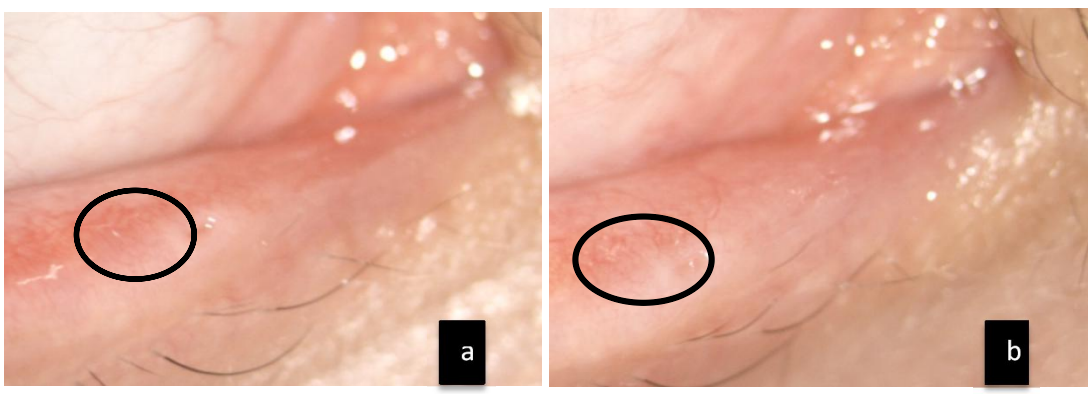

Table 1. Technical features of the Plexr device.	
Parameters	**Values**
Working gas Air	Air
Power supply	Docking station = 24 V
	Hand pieces: embedded inductive charger = 5
Hand pieces:	
Max output	≤ 2 W
Max working voltage	≤ 1.3 kVPP
Output frequency	(70–80) kHz
Hand piece types:	
White*	V peak to peak = 500 V, Power = 0.7 W, Frequency = 75 kHz
Green	V peak to peak = 600 V, Power = 1 W, Frequency = 75 kHz
Red	V peak to peak = 700 V, Power = 2 W, Frequency = 75 kHz
Maximum absorbed power	120 W
(Docking station)	
Applicator electrode	Stainless steel sterile disposable needle
Risk classification of the device	IIb**(Medium-high risk)
*In current study, the white hand piece was used. **This classification relates to the Non-invasive medical devices within the field of dermatology.	

To prove the effectiveness of the PANIS method, preoperative and postoperative evaluations were performed. Refractive parameters(UDVA, BDVA and refraction errors), noninvasive Schirmer test, tear meniscus height(TMH), tear break-up time(TBUT), corneal fluorescein staining(CFS), using a handheld ocular surface analyzer (OSA-VET, SBM Sistemi, Torino, Italy), intra ocular pressure (IOP) and contrast sensitivity(CS) with NEI standard, using the rebound ton-ometer (Icare Finland Oy, Vantaa, Finland) and Mars letter contrast sensitivity test (Mars Perceptrix, Chappaqua, New York, USA), respectively and OSDI questionnaire (grading 0-100) performed before punctal occlusion, 1 week, 1 month and 6 months afterward, for signs and symptoms of dry eye or any complications. Moreover slit-lamp examinations were performed every day during the first week after the procedure to check the reopening status.

3. Results:

Six eyes of six patients with moderate to severe DED were enrolled(Table 2). As expected refraction parameters, UCVA and BCVA showed no significant changes in the 6-month follow-up. All cases had significant rise up in tear break-up time. In 4 patients tear meniscus height increased clearly for the first week, following the closure of puncta for 2-5 days. Three cases had down-trended in corneal fluorescein staining for 2 grades and two cases had a decrease for 1 grade. It is noteworthy that all 6 patients had remarkable increase Schirmer test results. Patient's satisfactions were assessed by OSDI questionnaire whereas; mean score for post-operation evaluation was 11.15 in comparison with pre-operation mean score that is 40.82.

Table 2. Patient's characteristics and Parameters which examined before and after procedure

Case 1 68-year-old/Female OD											
Plasma time	UCVA (Decimal)	Ref			BCVA (Decimal)	TBUT	TMH	CFS Grade	schirmer	Icare	OSDI
		sphere	cylinder	Axis							
Pre-op	0.50	-2	-0.5	30	1	9	0.2	1	4	15	18.75
1 week	0.7	-1.25	0	0	1	13	0.2	0	14	13	0
1month	0.7	-2	-0.5	25	1	10	0.2	0	7	14	0
6month	0.7	-2	-0.5	25	1	12	0.2	0	9	14	0

Case 2 52-year-old/Female OS											
Plasma time	UCVA (Decimal)	Ref			BCVA (Decimal)	TBUT	TMH	CFS Grade	schirmer	Icare	OSDI
		sphere	cylinder	Axis							
Pre-op	0.05	-4	-6	100	0.1	10	0.2	2	6	14	43.18
1 week	0.05	-4	-6	100	0.1	12	0.3	1	8	10	28
1month	0.05	-3.5	-6	100	0.2	11	0.25	0	8	11	25
6month	0.05	-4	-5	90	0.1	13	0.3	0	9	13	20.45

Case 3

57-year-old/Male

OS

Plasma time	UCVA (Decimal)	Ref			BCVA (Decimal)	TBUT	TMH	CFS Grade	schirmer	Icare	OSDI
		Sphere	Cylinder	Axis							
Pre-op	0.5	-5	-2	10	0.8	9	0.2	0	6	8	45
1 week	0.5	-5.5	-1.5	10	0.9	19	0.2	0	8	18	18
1month	0.5	-6	-1.5	12	0.9	18	0.15	0	9	17	20
6month	0.5	-5	-2	180	0.9	17	0.3	0	8	13	25

Case 4

53-year-old/Female

OS

Plasma time	UCVA (Decimal)	Ref			BCVA (Decimal)	TBUT	TMH	CFS Grade	schirmer	Icare	OSDI
		Sphere	Cylinder	Axis							
Pre-op	0.3	-2	-2	130	0.6	3	0.2	2	3	18	35
1 week	0.5	-2	-2.5	120	0.7	9	0.3	1	11	16	2.77
1month	0.6	-2.5	-2.5	130	0.8	10	0.2	0	10	21	0
6month	0.6	-2.5	-2.5	120	0.8	10	0.3	0	13	16	0

Case 5

69-year-old/Female

OS

Plasma time	UCVA (Decimal)	Ref			BCVA (Decimal)	TBUT	TMH	CFS Grade	schirmer	Icare	OSDI
		Sphere	Cylinder	Axis							
Pre-op	0.5	-2	-0.5	150	1	6	0.15	2	4	12	63
1 week	0.7	-1.25	-0.5	150	1	14	0.3	1	13	12	21
1month	0.7	-2	-0.5	155	1	20	0.2	1	11	13	20
6month	0.7	-2	-0.5	160	1	13	0.2	1	10	16	18.7

Case 6

63-year-old/Female

OS											
Plasma time	UCVA (Decimal)	Ref			BCVA (Decimal)	TBUT	TMH	CFS Grade	schirmer	Icare	OSDI
		Sphere	Cylinder	Axis							
Pre-op	0.3	-3.5	-2	160	0.8	5	0.2	2	6	9	40
1 week	0.4	-3	-2	160	0.8	10	0.4	1	17	9	8.33
1month	0.4	-3	-2.5	163	0.8	6	0.2	1	13	9	3.5
6month	0.4	-3	-2	165	0.8	6	0.2	0	10	14	2.77

4. Discussion

Punctal occlusion is suggested as an alternative treatment for DED where artificial tears or oral medications no longer ameliorate signs and symptoms that cause complaints [3].whereupon , the efficacy of temporary punctal occlusion has been proved for treating DED after laser in situ keratomileusis (LASIK) [39]. One of the approaches for occluding punctum for a temporary period evaluated by James T. Patten, that has been used N-butyl cyanoacrylate tissue adhesive and the results indicated that the ocular surface dryness improved in a couple of days after the procedure [40]. Another study conducted by Farrell et al. proved that dissolvable collagen plugs can be effective on treating aqueous deficient dry eyes .[41] However, collagen plugs may conclude to epiphora as they are not producing total occlusion [1, 42]. Thus , dissolvable and reversible punctum plugs are good approaches to assess contraindications and face with patient's complications after permanent occluding [43]. Knapp et al. compared deep and superficial lacrimal puncta cauterization and found out that, punctum remained close in deeper thermal cautery more significantly [44].Nevertheless, the occluding procedure may be either overused or underused, sometimes permanent or congenital occluding should be reopen using a pigtail probe to prevent symptoms such as epiphora [45].

In recent years, plasma technology has spread in different fields of medicine. Plasma treatments in dermatology include treatment for atopic eczema, chronic wound healing, benign periocular lesions, etc. [46]. Another study revealed that using plasma can sublimate excess skin in upperlid and suggested this method as a non-surgical blepharoplasty [47].

In 2019, Nejat et al. exploited the useful attribute of plasma to assess the safety of applying plasma spots on the ocular surface. For this purpose, his team studied histopathological changings in rabbit model, one month and six months after plasma exposure. They revealed

that this novel technique is definitely safe for ocular surface under special circumstances. Thus, they worked on disorders such as conjunctivochalasis and conjunctival cyst and proved PANIS method's efficacy by following up patients over six months. In the current study the efficacy in temporary punctal occlusion evaluated using Plasma device. According to the present findings, the PANIS Method has been suggested as a novel, safe, simple, inexpensive, office-based method with short learning curve, and it can be an applicable simulator, for obtaining sure about what will happen after permanent occluding treatment.

It is noteworthy that, because of the novelty of this method our team was restricted to limited patient number, and of course it's more trustworthy to do clinical trial (CT) with big amount of cases to get definite results. In conclusion, we evaluated this novel method and satisfaction of every participant which is proved by comparison of examinations before and after procedure, showed that PANIS Method lead to good result for temporary punctal occlusion and it is a simple, effective, safe and reversible method to treat tear film deficiency.

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