



Research Article

PANIS Method: A Cutting-Edge Approach for Lid Margin and Periocular Benign Lesions

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Citation: Nejat F, Egdtedari S (2024) PANIS Method: A Cutting-Edge Approach for Lid Margin and Periocular Benign Lesions. J Med Biomed Discoveries 6: 128. DOI: <https://doi.org/10.29011/2688-8718.100128>

Received Date: 27 May, 2024; **Accepted Date:** 06 June, 2024; **Published Date:** 11 June, 2024

Abstract

Background: The aim of this study is to present a novel approach for the noninvasive, office-based removal of benign lid margin and periocular lesions. **Methods:** Fifty-nine eyes from 59 patients with benign lid margin and periocular lesions were included in this study, with an average age of 52.5 years. All lesions were eliminated using the white handpiece of the PLEXR PLUS device in the office, with the application of topical numbing cream. Plasma-assisted non-invasive surgery (PANIS) is defined as applying atmospheric low-temperature plasma to sublimate all parts of the lesions behind the slit lamp. Fifteen different periocular and lid margin lesions were targeted to evaluate the efficacy of the PANIS method. The average follow-up time for all participants was 16 weeks. Parameters, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), conjunctival injection, and irritation, were measured before and after the PANIS procedure. Photo slit-lamp examinations were also done at every visit. Patient satisfaction was assessed using a rating scale from 0 to 10, with answers to two questions about the novel procedure (PANIS). **Results:** Our findings demonstrate that the PANIS method can effectively remove periocular and lid margin lesions without any recurrence or complications, resulting in complete lesion clearance. The procedure does not have any significant effect on BCVA and IOP. However, conjunctival injection and irritation, including redness, inflammation, and tearing, mostly improved by three grades due to the elimination of the causative factors of lid margin lesions, which mold the globe. With the successful removal of lesions, all patients rated their satisfaction level as 9 to 10, indicating maximum cosmetic and functional satisfaction. **Conclusion:** The PANIS method introduces a novel approach for the safe, easy, effective, and office-based removal of benign periocular lid margin lesions, especially those in proximity to the lacrimal punctum and between the eyelashes, with minimal invasion to the functional parts of the eye.

Keywords: Benign lesions; Atmospheric low-temperature plasma; Periocular lesions; Noninvasive removal; lid margin lesions; PANIS method

Introduction

Acquired eyelid disorders are common disorders that are recognized during regular checkups by ophthalmologists and even dermatologists. These diseases are categorized into three basis groups: inflammatory, infectious, and neoplastic [1].

Medical management of these lesions will be oral antibiotics, ointment or injection of steroids. Benign ocular lid margin and periocular originate from dermis (Lipid aggregation and Melanotic growth), epidermis or adnexal structures (Inflammation, infection and cyst formation) [2]. In recent studies, 85% of lid margin lesions were benign [3]. The most common lesions are reported chalazion, squamous papilloma, and inclusion cyst [4]. The pathophysiological aspect of all lid margin and periocular diseases refers to Table 1 [5].

Epidermis	1. Seborrheic keratosis (SK)
	2. Dermatitis papulosa nigra (DPN)
	3. Inverted follicular keratosis
	4. Verruca vulgaris
	5. Molluscum contagiosum
	6. Squamous papilloma (Acrochordon or skin tag)
	7. Epidermal inclusion cysts/milia
	8. Cutaneous dermoid cyst
	9. Keratoacanthoma
	10. Cutaneous horn
Melanocytic	1. Ephelis (freckles)
	2. Lentigo simplex
	3. Solar Lentigo
	4. Nevi
Adnexal lesions	1. External hordeolum
Hair Follicles	1. Trichoepithelioma
	2. Trichofolliculoma
	3. Trichilemmoma
	4. Pilomatrixoma
Sweat Glands	1. Apocrine hidrocystoma (cyst of Moll)
	2. Eccrine hidrocystoma
	3. Trichilemmal (pilar) cysts
	4. Syringoma
	5. Pleomorphic adenoma
	6. Eccrine spiradenoma
Accessory Lacrimal Glands	1. Pleomorphic adenoma
	2. Oncoeytoma
Sebaceous Glands	1. chalazion
	2. Internal hordeolum (Meibomian gland)
	3. Cysts of Zeis
	4. Sebaceous cysts (steatocystoma)
	5. Sebaceous gland hyperplasia
	6. Sebaceous gland adenoma
Stromal Lesions	1. Xanthelasma
Vascular Lesions	1. Pyogenic granuloma
	2. Capillary hemangiomas
	3. Angiofibromas
	4. Nevus flammeus (port-wine stain)

Neurogenic	1. Plexiform neurofibroma
	2. Solitary neurofibroma
	3. eyelid schwannoma
Lipomatous	1. Lipomas

Table 1: Pathophysiological aspect of lid margin and periocular lesions.

Fifteen common lid margin and periocular lesions were included in this study, which are introduced below:

Acrochordon and skin tags

The common neoplasms of the skin are often accompanied by itching and pain. Hormone imbalance and obesity serve as cofactors for these papilloma-type lesions. Without histopathological tests, it is difficult to distinguish between Acrochordon and benign nevi. Some studies have reported the prevalence of these lesions to be as high as 46% in the general population. Skin tags are benign cosmetic concerns, being pedunculated and attached to the skin [6].

Lid margin and periocular Hemangioma

Two kinds of hemangiomas are common: cavernous and capillary. Capillary hemangioma is the most common orbital tumor of vascular origin and a benign neoplasm in the orbit [7]. Hormonal fluctuations can cause the formation of clusters of capillaries in endothelial cells, while trauma and inflammation can trigger this disorder [8].

Sebaceous Hyperplasia

In this lesion, the sebaceous gland structure is normal, with an increasing number prevalent in elderly adults. Hyperplasia appears as a white-yellowish lesion, usually after chronic immunosuppressive medication use [9,10].

Eccrine and Apocrine hidrocystoma

Hidrocystoma is a watery cyst that occurs in adulthood, mostly on the eyelid. These cysts have histopathological differences between the apocrine and eccrine types. Apocrine hidrocystomas are cystic neoplasms, while eccrine hidrocystomas are more likely to occur when sweat becomes trapped in a dilated duct or gland [11].

Lid margin Nevus

These common lesions vary in color, appearance, and location on the body and are prevalent in females (78%), with rare cases transforming into malignancies [12]. Any changes in size, border regularity, color, and symmetry should be considered signs of malignant transformation [13].

Inclusion cyst

Inclusion cysts are common benign epidermal cysts, mostly seen on the face and filled with keratin debris. These cysts may

also occur on the bulbar conjunctiva of the eye. While they are not harmful, untreated inclusion cysts can become inflamed and infected [14].

Papilloma

Human papillomavirus (HPV) can cause a benign type of tumor named papilloma, composed of squamous epithelium, and it is most commonly seen in patients aged 20-40 years. They typically present as exophytic, verrucous growths on the skin or mucous membranes [15].

Trichoadenoma

These are rare yellowish adnexal tumors composed of sebaceous glands and hair bulbs. They are usually less than 1 centimeter in size and grow very slowly [16].

Xanthelasma

These flat yellowish lesions are composed of lipid-laden macrophages (xanthoma cells) within the dermis. Xanthelasma is prevalent in about 4% of the global population [17].

Syringoma

These benign lesions are yellowish or skin-tone colored and typically appear in multiples, mostly on the lower eyelid. They are derived from eccrine sweat gland ducts and are composed of proliferating epithelial cells [18].

Verruca Vulgaris

This is one of the wart disorders associated with the human papillomavirus (HPV) and can be transmitted by skin-to-skin contact. Verruca vulgaris has an irregular shape and is more common in males [19].

Seborrheic keratosis

UV exposure and immunologic disorders can cause Seborrheic keratosis on hair-bearing parts of the skin. This is the most common epidermal tumor in dermatologic visits, appearing in oval or circular shapes, and varying in color from skin-tone to yellowish or brownish [20,21].

Benign lid margin and periocular lesions can be cosmetically bothersome. Before planning treatment, surgeons can assess the possibility of malignancy through patient history and clinical examination. Signs such as bleeding, rapid growth, and tenderness

may indicate the need for biopsy. Treatment modalities include conventional surgical methods for benign lid margin lesions, as well as recent options such as ultra-pulse CO2 laser, plasma exeresis, electrocautery, cryotherapy, and topical trichloroacetic acid. It is important to avoid causing harm to the functional parts of the eye during treatment [22-25].

In recent studies, atmospheric low-temperature plasma has been proven safe and effective in treating numerous ocular diseases, with successful treatment of more than 10 disorders. Plasma spots offer a noninvasive treatment modality utilizing a sublimation mechanism called plasma-assisted noninvasive surgery (PANIS). In this study, our aim is to evaluate the efficacy of a single session of PANIS treatment for the office-based removal of lid margin and periocular lesions.

Method

Patient selection

Fifty-nine patients, with an average age of about 52.5 years, 62.71% of whom are female, visited the Vision Health Research Center clinic in 2023. Fifty-nine eyes, comprising 35 right eyes and 24 left eyes, were diagnosed with benign lesions in the lid margin and periocular regions. All patients underwent evaluation through history-taking and complete clinical and slit-lamp examinations conducted by two expert ophthalmologists. After approval by the ethics committee of Semnan University of Medical Sciences, Semnan, Iran, and after our team explained all conditions of the PANIS treatment, including possible side effects or complications, participants signed the informed consent form and were included in all steps of the research.

PANIS Method

All patients were locally anesthetized with a topical numbing cream called Xyla-P (manufactured by Tehranchemie.CO, Tehran, Iran), which contains 2.5 g of prilocaine and 2.5 g of lidocaine in 100g of cream. The cream was applied to the lesion and the surrounding skin. Patients with lid margin lesions received three doses of tetracaine 0.5% eye drops (Sina Daro, Tehran, Iran) in the target eye, with a 5-minute interval before applying the numbing cream. All procedure steps were performed by one ophthalmologist (F.N.) behind the slit-lamp in an office-based manner. Plasma spots were applied using the white handpiece of the PLEXR PLUS device (manufactured by GMV, srl, Rome, Italy) directly on the lesion (Table 2). Ionizing the air between the tip of the needle of

the device and the targeted pathology can generate atmospheric low-temperature plasma, resulting in superficial sublimation (Supplementary Video 1).

In simple and flat lesions on the skin, including periocular hemangioma, seborrheic keratosis, syringoma, and xanthelasma, the surgeon applied plasma to sublimate the lesion layer by layer until ensuring that even the visible bottom of the lesion is removed by plasma spots. If any bleeding occurred during the removal of hemangioma, the surgeon stopped the bleeding with pressure, and the continuation of the treatment was postponed to the next session.

In pedunculated lesions such as acrochordon, lid margin papilloma, or nevus, periocular verruca vulgaris, and skin tag, the lesion is first caught with forceps. Plasma spots are then applied directly to the attached bottom of the lesion on the skin, and the process continues until the lesion is dissected, and all remaining, deeper-seated lesions are removed. The isolated tissue was sent for histopathological examination.

In cystic lesions such as sebaceous hyperplasia, eccrine hidrocystoma, apocrine hidrocystoma, and inclusion cyst, the first step involves applying commensurate spots of plasma to help open an aperture to evacuate any contents from the lesion. After complete discharge, a few plasma spots are applied to the bottom of the lesion to reduce the chance of recurrence.

In lesions that extend throughout the eyelashes, such as trichoadenoma, plasma spots are applied between the cilia to remove the lesion, in order to avoid cilia loss.

Measured parameters

Patients with lid margin lesions were evaluated for signs and symptoms such as conjunctival injection and irritation, assessed using photo slit-lamp (SL9900 ELITE 5X-D, CSO, Firenze, Italy). Furthermore, best-corrected visual acuity (BCVA) and intraocular pressure (IOP) were measured using a Topcon CT-80 non-contact tonometer (NCT) before and after complete healing of each patient following PANIS treatment [26]. Conjunctival injection and irritation were evaluated using two comprehensive references that defined the conjunctival injection grading system based on vasodilation patterns, including several, multiple, and total eye patterns. Irritation grading was based on three parameters: redness, inflammation, and tearing [27,28].

The device operates using air as the working gas.	
White handpiece	Peak to peak voltage of 500 V
	Power of 0.7 W
	Frequency of 75 kHz.
Green handpiece	Peak to peak voltage of 600 V
	Power of 1 W
	Frequency of 75 kHz
Red handpiece	Peak to peak voltage of 700 V
	Power of 2 W
	Frequency of 75 kHz
It is powered by a docking station with a voltage of 24 V.	
Handpieces	The maximum power output of the devices are 2 W.
	The maximum working voltage is 1.3 kVPP.
It employs a sterile disposable needle made of stainless steel as the applicator electrode.	

Table 2: PLEXR PLUS characteristics.

Result

This research included 59 eyes from 59 patients with an average age of 52.5 years old. Forty patients were candidates to undergo PANIS treatment for their lid margin lesions, while 19 persons were diagnosed with periocular lesions. In the lid margin lesions group, there were 28 right eyes and 12 left eyes, while in the periocular lesions group, there were 7 right eyes and 12 left eyes.

The measured BCVA and IOP did not show significant changes in neither lid margin and periocular lesions. However, three patients with papilloma and skin tags experienced an improvement of 1 line in BCVA. The hypothesis is that the effect of molding the globe with lesions may cause blinking issues, tearing, and fluctuations in vision.

Eleven patients with lid margin lesions experienced a 3-grade improvement in conjunctival injection, 11 patients experienced a 2-grade improvement, and 8 patients had a 1-grade enhancement. Ten participants did not show any signs of conjunctival injection before or after the PANIS procedure. Irritation enhancement was 3 grades for 12 patients, 2 grades for 8 persons, and 20 patients

did not experience any signs or symptoms of irritation. Irritation grades were based on redness, inflammation, and tearing. Some patients' lesions were small or not bothering the eye globe, so irritation did not occur in 20 patients.

The satisfaction parameter was assessed through two questions asked of patients after complete healing following PANIS treatment. The first question was: 'If you had the same disease in your other eye, would you prefer this treatment modality?' The second question was: 'If a close family member had the same disease, would you suggest this treatment modality for her/him?' Both questions were intended to assess satisfaction with both cosmetic and functional aspects. The answers ranged from 0 to 10, where 0 indicated minimum satisfaction and 10 indicated maximum satisfaction. All patients answered both questions with the highest level of satisfaction, and the average of the answers to both questions for all 59 patients was 9.9 (Table 3, Table 4).

All lesions were successfully and completely removed after a single session of PANIS treatment, with the exception of those in hemangioma patients without any recurrence or complications (Figure 1, Figure 2).

Diagnosis	Patients	BCVA		IOP		Conjunctival injection		irritation		Satisfaction
		Before	After	Before	After	Before	After	Before	After	
Acrochrdon	P1	10/10	10/10	15	15	3	0	2	0	10
	P2	10/10	10/10	12	12	2	0	0	0	10
	P3	10/10	10/10	16	16	3	0	3	0	10
	P4	10/10	10/10	15	15	3	1	3	0	10
	P5	9/10	9/10	11	11	3	0	2	0	9
Hemangioma	P6	10/10	10/10	12	13	1	0	0	0	10
	P7	10/10	10/10	11	11	2	0	1	0	10
Sebaceous Hyperplasia	P8	10/10	10/10	20	20	1	0	0	0	9
	P9	7/10	7/10	12	12	2	0	2	0	10
	P10	10/10	10/10	16	16	0	0	0	0	10
Eccrine Hidrocystoma	P11	10/10	10/10	15	15	1	0	1	0	10
	P12	9/10	9/10	19	19	2	0	3	0	10
	P13	10/10	10/10	11	11	1	0	0	0	10
	P14	10/10	10/10	16	16	3	1	3	1	10
	P15	9/10	9/10	12	12	0	0	0	0	10
Apocrine Hidrocystoma	P16	10/10	10/10	13	13	3	1	2	0	10
	P17	10/10	10/10	11	11	0	0	0	0	10
	P18	10/10	10/10	17	19	0	0	0	0	10
	P19	8/10	8/10	11	11	2	1	2	0	9
	P20	10/10	10/10	11	12	3	0	3	0	10
Lid Margin Nevus	P21	10/10	10/10	18	18	3	0	2	0	10
	P22	9/10	9/10	15	15	1	0	1	0	10
	P23	10/10	10/10	11	11	0	0	0	0	10
	P24	10/10	10/10	10	10	3	0	3	0	10
	P25	10/10	10/10	12	12	2	0	1	0	10
	P26	8/10	9/10	13	12	3	0	3	0	10
Inclusion Cyst	P27	10/10	10/10	13	14	3	0	3	1	10
	P28	9/10	10/10	11	10	2	0	3	0	10
Papilloma	P29	7/10+	7/10+	18	18	1	0	3	0	9
	P30	10/10	10/10	12	11	0	0	0	0	10
	P31	10/10	10/10	13	13	0	0	0	0	10
	P32	8/10	8/10	11	11	3	0	3	0	10
	P33	8/10	9/10	15	16	3	0	3	0	10
Trichoadenoma	P34	7/10	8/10	11	12	3	0	3	0	10
	P35	8/10	8/10	10	10	3	1	2	0	10

Outer Canthal Skintag	P36	10/10	10/10	15	14	1	0	0	0	10
	P37	7/10	8/10	11	11	2	0	1	0	10
	P38	10/10	10/10	11	12	0	0	0	0	10
	P39	10/10	10/10	10	10	0	0	0	0	10
	P40	9/10	9/10	16	15	0	0	0	0	10

Table 3: Measured parameters of Patients with lid margin lesions, before and after PANIS method.

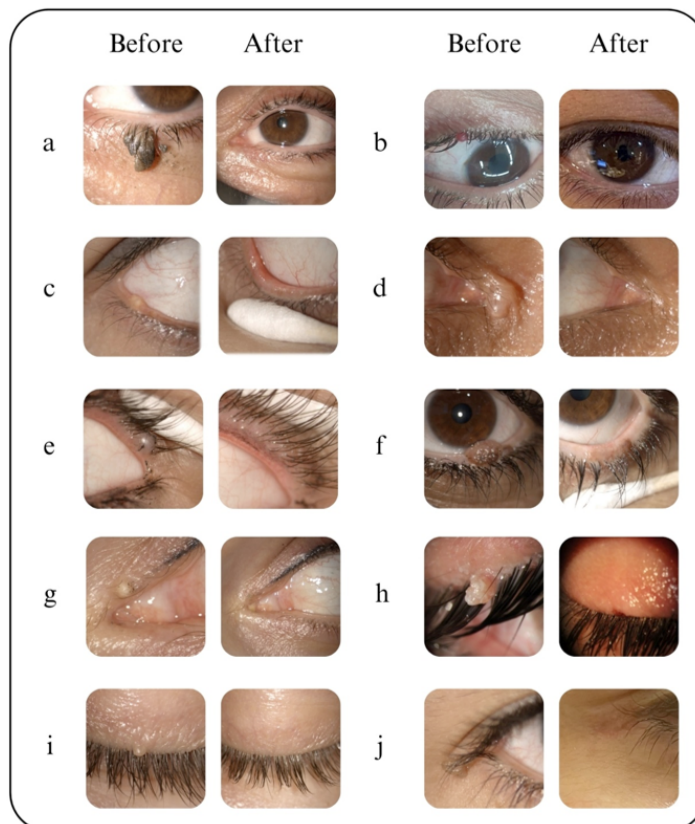


Figure 1: Before and after PANIS method for patients with lid margin lesions, a. Acrochordon, b. Lid margin Hemangioma, c. Sebaceous hyperplasia, d. Eccrine hidrocystoma, e. Apocrine hidrocystoma, f. Lid margin nevus, g. Inclusion cyst, h. Papilloma, i. Trichoadenoma, j. Outer canthal skintag

Diagnosis	Patients	BCVA		IOP		Satisfaction
		Before	After	Before	After	
Xanthelasma	P1	10/10	10/0	15	15	10
	P2	8/10	8/10	10	10	10
	P3	4/10	4/10	17	16	10
	P4	10/10	10/10	12	12	10
	P5	10/10	10/10	15	16	10
Hemangioma	P6	7/10	7/10	12	12	9
	P7	9/10	9/10	12	13	10

Syringoma	P8	6/10	6/10	9	10	9
	P9	10/10	10/10	18	15	10
	P10	9/10	9/10	11	11	10
	P11	8/10	8/10	15	13	10
	P12	10/10	10/10	12	12	10
Verruca vulgaris	P13	10/10	10/10	12	12	10
	P14	10/10	10/10	14	14	10
Seborrheic keratosis	P15	5/10	5/10	18	18	10
	P16	6/10	6/10	11	11	9
	P17	9/10	9/10	15	15	10
	P18	10/10	10/10	12	12	10
	P19	10/10	10/10	18	17	10

Table 4: Measured parameters of Patients with periocular lesions, before and after the PANIS Method.



Figure 2: Before and after PANIS method for patients with periocular lesions, a, b: Xanthelasma, c: Syringoma, d: Hemangioma, e: Verruca Vulgaris f: Seborrheic keratosis.

Discussion

A variety of lesions can affect the eyelid and periocular region, impacting both cosmetic appearance and functionality. It is vital to diagnose suspected lesions correctly and early through regular clinical visits and precise history-taking to avoid malignant transformation [29]. In pedunculated lesions such as acrochordon, large nevi, and papilloma, when it is easy to grasp the lesion with forceps, removal can be done by shave and snip excision, allowing for biopsy if necessary [30]. One study in 2020 indicated successful results with cryotherapy of upper eyelid after cutting squamous papilloma, using 30 seconds of freezing followed by 1 minute of thawing. [31]. Another conventional method is Electro cauterization, however this modality known as a surgical excision that may have a scar footprint on the skin [32].

The PANIS method was introduced in 2020, following two articles examining the histopathological changes in rabbit conjunctiva

exposed to plasma spots in 1-month and 6-month follow-up, proving the safety of atmospheric low-temperature plasma on conjunctiva. Additionally, measuring cytokine levels in tear and serum samples of a rat model, whose conjunctiva was exposed to plasma spots, showed no significant and persistent effects [33-35]. The PANIS method has been used to treat ocular surface diseases such as conjunctivochalasis, conjunctival cysts, dry eye disease, pinguecula, conjunctival concretion, pseudophakic bullous keratopathy, pterygium, and conjunctival nevus [36-46].

It's important to distinguish the treatment approach for lid margin and periocular lesions from those elsewhere on the skin. While these pathologies are often removed with shaving or iris scissors, using such tools near the delicate eye area in a conscious patient poses significant risks. Though surgical excision is the primary method for removing lid margin and periocular lesions, the PANIS method offers a less invasive and office-based alternative. We emphasize the importance of the PANIS method in treating benign

lesions proximity to the punctal and critical areas, as it preserves the functionally sensitive parts of the eye (Figure 3). The PANIS method is unique in its ability to save almost all cilia and allow for continued cilia growth. This study conducted to elucidate the roll of PANIS method in treating benign lid margin and periocular lesions with a safe, cost-benefit, effective and office-based modality, with less invasive damage to eye's functional organs. Accurate diagnosis of pathology is necessary for avoiding recurrence after a perfect treatment procedure. Although, a more extended follow-up period will be needed for more accurate inference.



Figure 3: Successful removal of Nevus on punctum after one session of PANIS.

Conclusion

The PANIS method appears to be an immensely effective, easy, safe, and cost-effective method with a short learning curve for achieving complete clearance of lid margin and periocular lesions, with minimal harm to the anatomy.

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

Funding: No funding to declare.

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

Acknowledgments: No one to declare.

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

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