

Varenicline Solution Nasal Spray 0.03 Mg for the Treatment of Dry Eye Disease Following Photorefractive Keratectomy

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Purpose: To evaluate the use of varenicline solution nasal spray 0.03 mg (VNS) as a treatment option for the signs and symptoms of dry eye disease following photorefractive keratectomy (PRK).

Patients and methods: Subjects electing to undergo PRK were randomized to VNS (study group) or vehicle (control group) twice daily and started treatment with VNS 28 days prior to surgery with continued use of the treatment for 84 days after PRK. After starting treatment, subjects were seen on the day of the procedure and postoperatively at days 2, 3, 4, 7, 28 and 84. The primary outcome measure was the mean change in NEI-VFQ-25, a dry eye item questionnaire, from baseline to day 84. The second primary outcome measure was the rate of corneal epithelial healing following PRK. Secondary outcome measures included eye dryness score (EDS), tear break up time and visual outcomes. The use of rescue therapy was also evaluated.

Results: Twenty-one subjects were enrolled in the study group, and twenty subjects were enrolled in the control group. Results from the NEI-VFQ-25 questionnaire revealed positive results in both groups and the between-group difference was not statistically significant ($P > 0.05$). There was a trend towards faster re-epithelialization in patients treated with VNS vs placebo, where 100% epithelial closure was observed by Day 3 in the VNS group versus Day 4 in the control group; however, the between-group difference was not statistically significant ($P > 0.05$). Three subjects had rescue therapy in the control group while a single subject was rescued in the study group. A higher rate of eyes achieved vision of 20/16 or better in the study group (82.5%) versus the control group (72.5%) at 3 months.

Conclusion: VNS is a favorable dry eye treatment option for patients following PRK, particularly in patients hoping to avoid additional topical medications or punctal occlusion. The higher percentage of eyes with UCDVA of 20/16 or better in the treatment group may suggest optimization of epithelial recovery after PRK.

Keywords: dry eye disease, dry eye syndrome, varenicline, neurostimulation, ocular inflammation, ocular pain

Introduction

Dry eye disease (DED) is the most prevalent complication following corneal refractive surgery, affecting a significant number of patients.¹ The disruption of corneal afferent innervation during procedures such as photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) has been recognized as an important factor thought to contribute to DED. The disruption in the sensory feedback to the lacrimal functional unit can result in symptoms such as fluctuating vision and foreign body sensation in the eye.² These symptoms can markedly diminish a patient's quality of life and negatively impact their perception of refractive surgery. Notably, prior work has demonstrated 90% of patients report some signs of DED immediately after refractive surgery and 60% still report symptoms 1 month after surgery.²

Advancements in treatment modalities for DED have led to more options and the ability to provide more individualized care to patients in the post-refractive setting. The overarching goal of all treatments is to alleviate symptoms and restore the health of the ocular surface. These options include novel topical therapies,³⁻⁶ meibomian gland treatments⁷ and recently, a novel nasal spray containing varenicline solution, also known as TYRVAYA[®] (Oyster Point Pharma Inc.),

which was FDA approved in 2021 for the signs and symptoms of DED.^{8,9} VNS is a pharmacologic option in the novel category of neurostimulation that aims to stimulate natural tear production. VNS increases basal tear production by targeting receptors on trigeminal nerve terminating in the nasal cavity, thereby activating tear production through the parasympathetic pathway.^{8,10}

There has been heightened interest in the perioperative treatment of the ocular surface in patients undergoing corneal refractive procedures, including PRK, LASIK and small incision lenticule extraction (SMILE) to improve surgical outcomes.^{11–13} This present study aims to evaluate the efficacy of VNS as a treatment for the signs and symptoms of dry eye in subjects undergoing PRK. This study aligns with the growing interest in proactive and comprehensive management strategies to enhance the overall outcomes of refractive surgeries.

Methods

This prospective, randomized, double-masked clinical trial (NCT05045508) was conducted at a single site in Omaha, NE. It adhered to the principles of the Declaration of Helsinki and received approval by the WCG Institutional Review Board. All participants provided written informed consent.

Patient Selection

Myopic patients planning to undergo PRK were enrolled in the study. Subjects were recruited from a local population of patients presenting for refractive surgery evaluation. The inclusion and exclusion criteria for the study are summarized in Table 1.

Randomization, Treatment and Data Collection

Subjects were randomized into two groups in a 1:1 ratio using a web-based randomization sequence. The study group administered an application of VNS twice daily and the control group administered an application of placebo (vehicle) nasal spray twice daily. Both groups started the nasal spray 4 weeks prior to PRK and continued for 84 days (approximately 3 months) following the procedure. The day of surgery (Day 0) was established as the baseline for assessing study outcomes. Following Day 0, subjects were seen at days 2, 3, 4 and 7 to evaluate rates of corneal epithelial healing. Following the day 7 visit, subjects were seen on days 28, 84 and 168 (approximately 6 months).

Table 1 Key Inclusion and Exclusion Criteria are Shown. MRSE = Manifest Refractive Spherical Equivalent

Criteria Type	Description
Inclusion Criteria	
Age	≥18 years
Refractive Status	Myopic patients undergoing PRK; MRSE between −1.00D to −6.00D; ≤2 D difference between the two eyes
Drug Administration	Ability to independently administer the study drug
Dry Eye History	No history of dry eye
Exclusion Criteria	
Corneal Integrity	Presence of non-healing corneal epithelial defects or ulcers
Punctal Plugs	Use of temporary punctal plugs in the last month or presence of permanent punctal plugs
Corneal Pathology	Any pathology potentially interfering with LASIK outcomes
Surgical History	Prior refractive surgery, infectious keratitis within 3 months, ocular inflammation or macular edema, nasal/sinus surgery, nasal CPAP use, blepharoplasty, corneal transplant
Drug Sensitivity	Known hypersensitivity to study drug components
Medication	Current use of nicotinic acetylcholine receptor agonists (eg, Nicoderm®, Chantix®)

There were two main outcome measures. The first main outcome measure was the mean change in the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) score from Day 0 to Day 84 (3 months). The second main outcome measure was the mean change in corneal epithelial healing rate from Days 2 to 7 as evaluated by a masked provider. All of the outcome measures including the primary and secondary outcome measures evaluated in this study are shown and listed in Table 2.

Each subject underwent a standard PRK surgical technique, which included removal of the central 8 mm of the corneal epithelium. Use of Mitomycin C was not employed for the purpose of this study. A bandage contact lens was placed at the conclusion of each procedure.

Two subjective, self-administered, previously validated questionnaires were employed in this study. The first was the NEI-VFQ 25, a 25-item validated questionnaire designed to assess the impact of visual impairment on the patient's health-related quality of life, with a focus on symptoms of ocular irritation. The questionnaire was scored from 0 (worst) to 100 (best) and was administered at days 0, 28, 84 and 168. The second assessment was the Eye Dryness Score (EDS), which attempts to quantify patient discomfort based on a visual analogue scale ranging from 0 (no discomfort) to 100 (max discomfort). EDS was specially developed for dry eye disease clinical trials and was administered at all study visits.

Rescue Criteria

Rescue criteria were established to provide guidance for additional interventions related to the treatment of DED. If subjects required use of artificial tears more than or equal to 4 times daily following removal of the bandage contact lens, they met the criteria for rescue therapy. Rescue therapy options included additional preservative-free artificial tears, prescription dry eye therapy (eg, topical cyclosporine or lifitegrast) or punctal plugs in the upper or lower punctum.

Study Drug: Varenicline Solution Nasal Spray (VNS)

The VNS nasal spray mechanism facilitates the administration of a preservative-free, intranasal formulation containing 0.03 mg of varenicline. Varenicline is a highly selective nicotinic acetylcholine receptor agonist (nAChR) and targets the trigeminal parasympathetic pathway, which stimulates the nerves innervating the lacrimal function unit. This pathway is likely responsible for one-third of the basal tear film production and activation of this pathway represents a novel approach to improving the signs and symptoms of dry eye disease.

Table 2 The Primary and Secondary Outcome Measures are Displayed

Outcome Type	Measure	Description	Time Points
Main Outcome Measures			
NEI VFQ-25 Score	Primary	Mean change in NEI VFQ-25 score	Day 0 to Day 84 (3 months) postoperative
Mean change in corneal epithelial healing	Primary	Rate of corneal epithelial healing rate as measured by masked provider	Day 2 to Day 7
Secondary Outcome Measures			
Eye Dryness Score (EDS)	Secondary	Mean change in EDS (Visual Analogue Scale)	Day 0 to Day 84
Tear Break-Up Time (TBUT)	Secondary	Mean change in TBUT	Days 28 and 84
Residual Refractive Error	Secondary	Measurement of residual refractive error	Days 28 and 84
Rescue Treatment/Punctal Plugs	Secondary	Proportion requiring additional treatment or plugs	Day 84 and Day 168
Safety Evaluation			
Adverse Events	Safety	Number and severity of adverse events	Each study time point

Table 3 Baseline Characteristics for Both the Study and Control Populations are Shown

Parameter	VNS (n=21)	Vehicle (n=20)
Age, years (Mean, SD)	31.4 ± 6.7	34.0 ± 6.6
Gender (M/F)	10 F / 10 M	10 F / 10 M
NEI VFQ-25 score	91.2 ± 5.4	90.0 ± 6.1
Eye Dryness Score (EDS)	4.0 ± 6.8	6.3 ± 7.4
Tear osmolarity (mOsm/L)	302.9 ± 11.8	299.6 ± 13.6
Tear break up time (TBUT), secs	11.5 ± 7.6	9.3 ± 6.1

Statistical Analyses

An analysis of covariance (ANCOVA) model was used to compare VNS and placebo in the mean change from baseline at a certain time point (Day 84 or Day 128) for different efficacy endpoints (eg NEI VFQ-25, Corneal Fluorescein Staining, EDS). The ANCOVA model includes treatment as the fixed effect and baseline endpoint value as the covariate. Statistical analysis was performed using SAS[®] (SAS Version 9.4., SAS Inc., NC, USA). A p value less than 0.05 was considered to be statistically significant.

Results

Patient Demographics

Forty-one subjects were enrolled in the study, including 21 subjects in the study arm and 20 subjects in the control arm. The baseline characteristics of the study and control groups are shown in Table 3.

The mean baseline NEI-VFQ-25 score was 91.2 ± 5.4 in the study group and 90.0 ± 6.1 in the control group. At day 28 (1 month), the mean score in the study group was 94.1 ± 5.0 and 94.3 ± 4.6 in the control group ($P > 0.05$). At day 84 (3 months), which represents the first primary endpoint, the mean score in the study group was 97.0 ± 1.8 and 96.3 ± 2.4 in the control group ($P > 0.05$). These results are displayed in Figure 1.

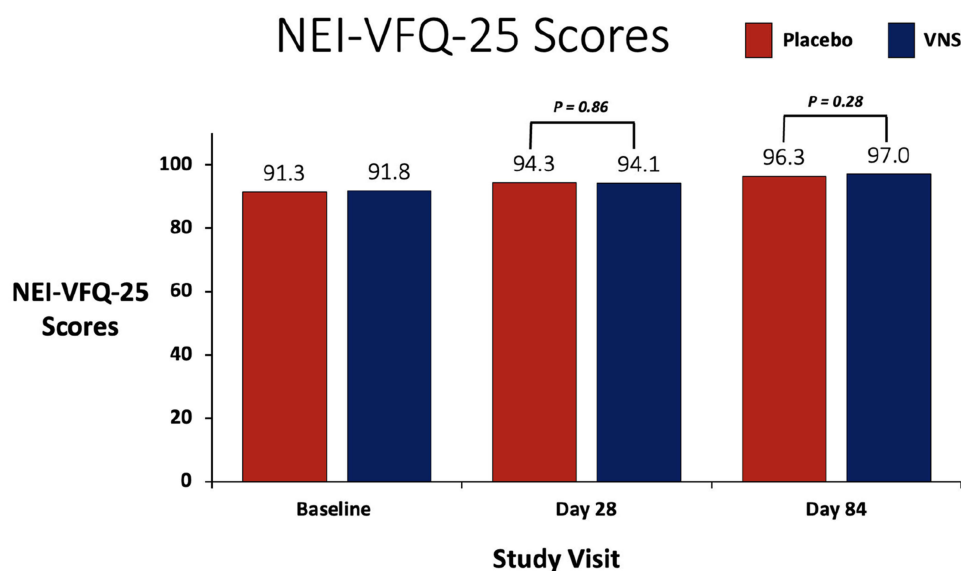


Figure 1 The NEI-VFQ-25 scores are shown at each key study time point. The between-group-comparison P values are shown to compare the study and control (placebo) group at days 7 and 84 in comparison to baseline (day of surgery).

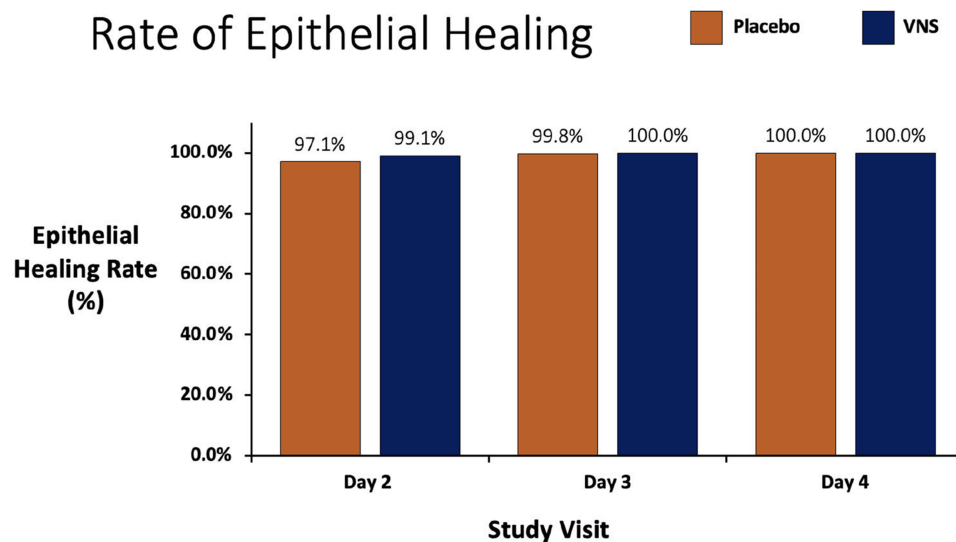


Figure 2 The rate of epithelial healing (closure of epithelium) is shown for each group. Epithelial healing was measured by estimating the area of an equivalent rectangle by a masked physician. 100% implies the epithelium was completely healed.

As measured by the VAS, the mean baseline EDS score was 4.0 ± 6.8 for the study group and 6.3 ± 7.4 for the control group. At day 84, in comparison to baseline, the mean change in the study group was -0.8 ± 20.7 , and in the control group the mean change was -6.9 ± 12.6 . The between-group comparison was not statistically significant ($P > 0.05$).

For tear break-up time (TBUT), the mean baseline value was 11.5 ± 7.5 in the study group and 9.3 ± 6.1 in the control group. At day 28 (1 month), the mean TBUT value was 13.7 ± 8.4 in the study group and was 10.4 ± 3.4 in the control group. At day 28, the between-group comparison was not statistically significant ($P > 0.05$). At day 84 (3 months), the mean TBUT value was 13.7 ± 9.1 in study group and 11.1 ± 9.3 in the control group. At day 84, the between-group difference was not statistically significant ($P > 0.05$).

The mean change in epithelial healing rate was compared between the two groups at postoperative time points within the first 7 days following PRK. At day 2, 99.1% of eyes had achieved complete healing of their epithelium in the study group, while 97.1% of eyes in the control group had achieved complete healing. At day 3, 100% of eyes in the study group had achieved complete healing of their epithelium, while 99.8% of eyes in the control group achieved complete healing. By day 4, 100% of eyes in both groups had achieved complete epithelial healing. Overall, there was a faster rate of epithelial healing in the study group, but the between-group difference was not statistically significant at Days 2 or 3 ($P > 0.05$). These results are shown in Figure 2.

Visual Outcomes

At 1 month, 92.5% of eyes were 20/20 or better in the study group, and 90% of eyes were 20/20 or better in the control group. At 3 months, in the study group, 97.5% eyes were 20/20 or better and 82.5% of eyes were 20/16 or better. In the control group, 97.5% of eyes were 20/20 or better and 72.5% of eyes were 20/16 or better. Although the study group had higher rates of eyes achieving 20/20 or better at each time point, this difference was not statistically significant ($P > 0.05$).

Safety and Rescue Therapy

There were no reported adverse events in either arm. The rate of rescue therapy (eg, additional dry eye therapy) was required more in the placebo group, with 3/21 subjects undergoing punctal plug instillation while a single subject had punctal plugs implanted in the study group.

Discussion

To the best of our knowledge, this present study represents the first study to investigate the use of VNS in treating the signs and symptoms of DED following PRK, a procedure associated with dry eye symptoms in the early postoperative period.¹⁴ PRK and

other corneal refractive procedures are commonly associated with dry eye disease in the postoperative setting, and the results of this study suggest VNS could be a treatment option for reducing the signs and symptoms of DED following PRK.

Recent studies have firmly established the significant impact of dry eye and ocular surface disease on surgical outcomes.^{13–15} Within the realm of refractive surgery, several mechanisms have been identified as contributors to the onset of dry eye. These include damage to corneal nerves, decreased blinking frequency, and possible alteration of the tear film dynamics owing to changes in the shape of the cornea.¹¹ Owing to the re-innervation that is observed following refractive surgeries such as PRK and the typical course being transient in nature, this is the likely main driver of signs and symptoms.¹⁶ With corneal nerve damage, there can be a reduction in natural tear production, which can not only impact quality of vision but can also impact healing in procedures that involve removal of the epithelium-like PRK. The use of VNS to combat the reduced tear production represents a promising alternative treatment option. This approach stimulates natural tear production and circumvents the complications associated with frequent instillation of topical eye drops, providing a more natural solution to managing dry eye in this phase of healing.

A similar study was performed evaluating the use of VNS following LASIK and was recently published.¹⁷ Similar to the results of this study, this aforementioned study did not find statistically significant results favoring the use of VNS versus placebo but did report trends showing directional improvement in dry eye parameters such as tear osmolarity, Schirmer test scores and fluorescein staining. Although this study was similar in design, LASIK does not involve removal of the corneal epithelium, and this study sought to also understand how healing after PRK is affected by the use of VNS by evaluating the change in epithelial healing rate and visual outcomes of patients. Further, it is well established that symptoms of dry eye following LASIK and PRK arise from a disruption of sensory input into the lacrimal gland system from damage to corneal afferent nerves.¹⁸ However, the pattern of nerve damage and recovery differs between LASIK and PRK, which likely contributes to a difference in ocular surface manifestations following the procedure.¹⁹

Studies leading to the approval of VNS demonstrated that twice-daily administration of the nasal spray provides a fast and clinically significant improvement in the signs and symptoms of DED over a 4-week period.^{8,20} A follow-up study evaluating signs and symptoms over 12 weeks was also performed and reported similar findings, demonstrating that the efficacy is maintained over an extended time period.⁹ This present study was unique from those aforementioned studies as it did not require a confirmed diagnosis of dry eye disease and aimed to enroll a real-world cohort of patients seeking corneal refractive surgery.

As a small study, the results of this study did not demonstrate a clear statistical benefit favoring the use of VNS versus placebo for the primary and secondary endpoints of this study. Despite the absence of a clear statistical benefit, the results of this study may still convey clinical significance and inform clinicians caring for patients in the perioperative period undergoing corneal refractive procedures such as PRK. In this study, the rate of healing was overall faster in the study group, and patient-reported symptoms as part of EDS and VFQ-25 demonstrated a directional improvement over the course of the postoperative period, favoring the study group. Furthermore, the proportion of patients achieving 20/16 or better vision was higher in the study group, suggesting VNS may assist in the epithelial remodeling and healing process, a critical part of the healing response following PRK. Moreover, more subjects required rescue therapy in the control group ($n = 3$) versus the study group ($n = 1$).

There are a multitude of treatment options to address DED symptoms in refractive surgery patients, including a number of topical options. However, there are known challenges with topical eye drops, and many patients electing to undergo refractive surgery are on existing topical regimens and not interested in adding to their existing medication burden. Topical immunomodulators remain a common option for treating dry eye in the perioperative setting with refractive surgery, but this represents another topical medication and there are well-established issues with tolerability with these agents.²¹ VNS is an attractive treatment option for those patients seeking a dry eye treatment that does not represent an additional topical medication. The simplicity of administration twice daily in each nostril carries a lot of advantages for patients, including mitigation of the treatment burden of an additional topical medication. Patients with poor dexterity, proprioception difficulties, tremors or cosmetic makeup concerns would also benefit from a treatment option that does not involve instillation of a topical agent. Furthermore, the recent outbreak of serious adverse events including infectious keratitis associated with contaminated topical eye drops will likely influence patients to seek alternative dry eye treatment options beyond a topical artificial tear or medicated eye drop.²² As a relatively new category of dry eye treatment, VNS is an attractive option as it avoids the issues specific to topical medication use including preservatives burning upon instillation and risk of contamination.^{23,24} Moreover, owing to the epithelial defect created

for the purpose of the procedure, patients undergoing PRK are at a heightened risk of infection and may benefit from a treatment to facilitate healing that is not associated with risk of contamination.

The use of VNS is relatively new in the treatment of dry eye and represents the first nasal spray dry eye treatment option. The safety profile of the device has been well established by large, prospective clinical trials, with the most common side effect being sneezing following instillation.^{8,25} Due to VNS being a relatively new agent, there are no long-term safety data available to date. Further, given the mechanism of action and lack of safety issues to date, it is unlikely that long-term use of VNS would cause damage to the nasal mucosa as it is not a vasoconstrictive agent.²⁶

This study is not without limitations. A sample size calculation was not performed, and the sample size was relatively small in each group. Although the results trended toward favoring the study group, the overall results of this study did not demonstrate a clear statistical benefit favoring VNS. The long-term consequences of use of VNS have not been entirely established. This study enrolled subjects with healthy baseline dry eye disease parameters, which may have contributed to the lack of clear benefit in the study group. Despite these limitations, this study provides real-world evidence evaluating the use of VNS as a treatment option for DED following PRK.

Conclusion

The challenges of topical medication use are widespread and recognized by clinicians caring for ocular surface disease and dry eye. VNS represents an attractive option for patients and clinicians hoping to avoid topical medications, and the results of this study provide real-world evidence supporting VNS as a favorable option for patients undergoing PRK. Further investigation is warranted, but this treatment option could represent a non-topical option for managing DED and optimizing outcomes in patients undergoing PRK.

Data Sharing Statement

The data set collected and analyzed for this present study is available from the corresponding author per reasonable request.

Ethics Approval

This study was approved by the WCG Institutional Review Board. All procedures conducted were in accordance with the WCG IRB and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained for each subject prior to the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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