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Efficacy and Safety of Miebo® (Perfluorohexyloctane Ophthalmic Solution) in Treating Dry Eye Disease - a narrative review

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Abstract

Introduction: Dry eye disease (DED) is a prevalent and debilitating ocular condition characterized by discomfort, visual disturbances, and tear film instability. Recent therapeutic developments have introduced perfluorohexyloctane ophthalmic solution (Miebo®) as a potential treatment for DED, particularly in patients with meibomian gland dysfunction (MGD).

Aim of the Study: This narrative review aims to evaluate the efficacy and safety of Miebo® in treating DED based on current clinical evidence.

Materials and Methods: A comprehensive literature search was conducted in PubMed, Embase, and Cochrane Library databases up to May 2024 resulting in the identification of 9 studies. The review included randomized controlled trials, prospective cohort studies, and systematic reviews that focused on the use of Miebo® for DED. Data on efficacy in improving tear film stability and symptom relief, as well as safety profiles, were extracted and analyzed.

Results: The evidence indicates that Miebo® significantly enhances tear film stability and alleviates symptoms of DED, with pronounced benefits observed in patients with MGD. Comparative studies demonstrate that Miebo® is more effective than conventional treatments, such as artificial tears and lipid-based formulations. Safety assessments reveal minimal ocular surface discomfort and no significant systemic adverse events associated with Miebo® use.

Conclusion: Miebo® shows substantial efficacy and a favorable safety profile in managing DED, making it a valuable therapeutic option, particularly for patients who do not respond to traditional therapies. However, further research is needed to confirm its long-term effectiveness and safety.

Keywords: Dry eye disease, perfluorohexyloctane, Miebo®, meibomian gland dysfunction, efficacy, safety.

Introduction

The ocular surface refers to the outermost layer of the eye, which includes the cornea, conjunctiva and eyelids (Nelson et al., 2017). It is a complex and delicate system that is responsible for maintaining the health and function of the eye (Craig et al., 2017). One common problem that can affect the ocular surface is dry eye disease, which is a

multifactorial condition that occurs when the eye does not produce enough tears or the tears produced do not have the correct balance of water, mucus and oil, where inflammation, hyperosmolarity and neurosensorial abnormalities could coexist (Stapleton et al., 2017). This condition arises due to inadequate tear production or excessive tear evaporation, leading to instability of the tear film and subsequent inflammation of the ocular surface (Lemp et al., 2012). DED can be caused by a variety of factors, including aging, certain medications and environmental conditions, such as prolonged use of the digital screens or living in a dry or dusty environment, or it can be related to autoimmune syndromes, like Sjögren syndrome (J. M. Sánchez-González et al., 2023).

DED presents a complex challenge in ophthalmology, with symptoms ranging from ocular discomfort to potential damage to the ocular surface. These symptoms include burning, itching, redness, and sensations of dryness, grittiness, or having a foreign body in the eye. In severe cases, DED can lead to vision problems, corneal damage, and even blindness (Bron et al., 2017; Huh et al., 2019). Affecting a substantial segment of the global population, its prevalence (ranged from 5 to 50%) (Stapleton et al., 2017) varies by age, gender, and geographic location (Bron et al., 2017). As of 2023, over 16 million adults in the United States were reported to be affected by DED (Bradley et al., 2019).

The tear film, comprising lipid, aqueous, and mucin layers, plays a pivotal role in maintaining ocular surface health and visual acuity (Tomlinson et al., 2011). Dysfunction of the meibomian glands, responsible for lipid secretion, significantly contributes to increased tear evaporation and tear film instability (Baudouin et al., 2016), exacerbating symptoms such as burning sensations, eyelid itching, tearing, dry sensation or foreign body sensation (Pisella & Pouliquen, 2002). MGD is a common and chronic disorder that has a significant adverse impact on patients' quality of life. It is a leading cause of evaporative dry eye disease (Lemp et al., 2012; Rabensteiner et al., 2018). Approximately 86% of people with DED have excessive tear evaporation associated with MGD (Lemp et al., 2012).

Effective treatment of DED requires an accurate diagnosis and a personalized treatment plan. The most common subjective method for diagnosing DED involves questionnaires and self-reported tests, such as the Ocular Surface Disease Index (OSDI) or the Dry Eye Questionnaire (DEQ) (Wolffsohn et al., 2017). While these tools are helpful for identifying the presence of DED, they rely on self-reported symptoms and may not accurately reflect the true severity of the condition (Wolffsohn et al., 2017). Traditional objective tests

include the Oxford grading system with fluorescein or lissamine green stains, the tear break-up time test (TBUT), and the Schirmer test (I and II) (Nelson et al., 2017; Wolffsohn et al., 2017) . Additional diagnostic options include measuring the tear meniscus (Rocha-De-Lossada et al., 2021) , evaluating metalloproteinases (Huh et al., 2019) , and assessing tear osmolarity (Lemp et al., 2011). Recently, a new device called the Ocular Surface Analyzer (OSA) has been developed to enhance the diagnosis and management of DED. The OSA is a non-invasive, objective tool that uses interferometry to measure the thickness and surface profile of the tear film, similar to a Keratograph (M. C. Sánchez-González et al., 2022).

Current therapeutic strategies for this condition include intense lubrication with tear substitutes to reduce hyperosmolarity and corneal nociceptor stimulation; contact lens bandaging; anti-inflammatory agents like corticosteroids or immunomodulators (cyclosporine, lifitegrast) to reduce inflammation and enhance tear stability; serum and platelet derivatives to promote healing and nerve regeneration; and systemic analgesics or anti-neuropathic drugs, such as antiepileptics or antidepressants (Giannaccare et al., 2022) . Results of the study “Effects of physical activity/exercise on tear film characteristics and dry eye associated symptoms: A literature review” shows that despite of a high heterogeneity in the studied population, study designs and methods, the current body of evidence suggest a positive association between exercise and improved tear volume, tear osmolarity, tear film stability, and relief from DED symptoms. Nevertheless other factors, such as reduced screen time during exercise, might contribute to symptom relief. (Navarro-Lopez et al., 2023) . However, managing DED remains challenging due to variations in patient response and the chronic nature of the disease.

Recently, perfluorohexyloctane (PFHO) ophthalmic solution (Miebo®) has emerged as a novel therapeutic option for DED. Utilizing perfluorocarbon technology, Miebo® stabilizes the tear film and promotes corneal epithelial healing (McDonald et al., 2016; Sheppard et al., 2014) . PFHO is a water-free, preservative-free, single-ingredient prescription eye drop approved to treat the signs and symptoms of DED (Sheppard et al., 2023a). Clinical investigations have shown promising results, indicating potential benefits in both objective assessments of ocular surface health and subjective relief of symptoms. There remains a clear need for more effective and targeted therapies addressing the underlying mechanisms of DED. The proper management of DED should be tailored to the specific cause of the condition and should address the fundamental mechanisms of the disease (e.g.,

excessive evaporation or aqueous deficiency) to reestablish tear film stability and ensure ocular surface homeostasis. Miebo® specifically targets tear evaporation and is the first and only FDA-approved treatment to treat the signs and symptoms of DED, making it particularly relevant for patients with DED [25]. Initial findings suggest that Miebo® demonstrates a significant ability to carry oxygen, potentially minimizes friction during blinking, and quickly disperses across the tear film surface to form a monolayer that reduces evaporation. These properties can help stabilize the tear film, aiding in the healing of the ocular surface. (Sheppard et al., 2023a).

This review aims to critically assess the current clinical evidence on the efficacy and safety of Miebo® in treating DED. By synthesizing data from randomized controlled trials, prospective cohort studies, and systematic reviews, we aim to provide insights into Miebo's® therapeutic potential and its evolving role in managing DED. Given the rising prevalence of DED and the limitations of existing treatments, innovative therapies like Miebo® hold promise for improving patient outcomes and quality of life.

In conclusion, this review aims to offer a comprehensive understanding of Miebo's® efficacy and safety profile, providing valuable insights into its potential to address unmet needs in the management of DED (Baudouin et al., 2013).

Clinical evidence

The efficacy and safety of Miebo® in treating DED have been evaluated in several clinical studies. One significant trial, The SEECASE study (Tauber et al., 2021), a phase 2 multicenter trial conducted under double-masked conditions, aimed to assess the efficacy, safety, and tolerability of twice daily (BID) or four times daily (QID) PFHO instillation compared to isotonic saline for the management of signs and symptoms associated with DED. The study cohort predominantly comprised females with a mean age of 53 years. At 8 weeks, both PFHO dosing arms demonstrated significantly greater improvements from baseline in mean total corneal fluorescein staining (tCFS) and mean visual analog scale (VAS) scores for eye dryness compared to the isotonic saline (0.9%) arm. Moreover, the QID dosing regimen exhibited superior improvements compared to BID dosing. For the Eye Dryness Score, changes from baseline were statistically significant compared with those of the control at week 8 [$P < 0.001$ (QID) and $P = 0.002$ (BID)]. Benefits on tCFS and symptoms started at 2 weeks after start of treatment and were maintained over the study duration. Overall, PFHO

treatment was well tolerated across both dosing schedules, characterized by low incidences of ocular adverse events (e.g., blurred vision, eye irritation, eye pain).

Additionally, a systematic review published in 2023, following PRISMA guidelines, summarized various studies evaluating perfluorohexyloctane (PFHO) as a treatment for dry eye disease (DED) (Ballesteros-Sánchez et al., 2023). The review highlighted consistent findings across multiple clinical trials, suggesting that PFHO-based treatments, including the commercial product Miebo®, significantly improve DED symptoms. These improvements were evident in several key metrics such as the Ocular Surface Disease Index (OSDI) scores, tear breakup time (TBUT), lipid layer thickness (LLT), and overall tear film stability. Furthermore, patient satisfaction was notably high, with minimal treatment-emergent adverse events reported, underscoring the safety and effectiveness of PFHO in managing DED. The review emphasized the potential of PFHO as a reliable therapeutic option, contributing to a growing body of evidence supporting its use in clinical practice.

Futhermore a randomized controlled study investigated the impact of water-free perfluorohexyloctane eye drops on tear film thickness (TFT) in patients with dry eye disease (DED). Forty-eight patients with mild to moderate DED were randomly assigned to receive either perfluorohexyloctane or unpreserved saline eye drops (Hydrabak®) four times daily for four weeks. The study found that perfluorohexyloctane eye drops temporarily increased TFT immediately after a single drop instillation and gradually increased TFT with repeated use, reaching a maximum effect at the end of the four-week period. Additionally, lipid layer thickness (LLT) increased more significantly in the perfluorohexyloctane group compared to the saline group. Other parameters improved in both treatment groups, but without significant differences between them. The results demonstrate that perfluorohexyloctane eye drops effectively increase both TFT and LLT over time, supporting their role in preventing evaporation and stabilizing the lipid layer of the tear film.(Schmidl et al., 2020).

GOBI (Tauber et al., 2023) was a phase 3, multicenter, double-masked randomized controlled trial designed to assess the effectiveness and safety of PFHO treatment compared to a hypotonic (0.6%) saline control for managing signs and symptoms in 597 patients diagnosed with DED and clinical indications of MGD over a treatment period of 2, 4, and 8 weeks. The study predominantly enrolled female participants, with approximately half of them aged 65 years or older. Both primary endpoints of the GOBI trial were achieved,

demonstrating significantly greater improvements in total corneal fluorescein staining (tCFS) scores and VAS dryness scores from baseline in patients treated with PFHO compared to those receiving hypotonic saline treatment at the 8-week mark. Mean improvements from baseline with PFHO treatment were notably higher across all key secondary endpoints, including changes in VAS dryness and tCFS scores by week 2, and changes in VAS burning or stinging scores and central CFS (cCFS) scores by week 8. Additionally, compared to the hypotonic saline group, the mean change from baseline in VAS dryness score in the PFHO group was statistically significant at weeks 2 and 8, though the difference was not significant at week 4. A higher percentage of patients in the PFHO group (41.2%) were classified as tCFS responders (defined by a ≥ 3 -step improvement in tCFS score) compared to those in the hypotonic saline group (27.2%). Similarly, 57.4% of patients in the PFHO group were considered responders for eye dryness (defined by a $\geq 30\%$ reduction in VAS dryness score), while 46.6% of those in the hypotonic saline group met the same criterion. Overall, PFHO treatment was well-tolerated and deemed safe. Reported ocular adverse events (AEs) in both treatment arms were mostly mild, with none categorized as severe. Ocular AEs were attributed to treatment in 6.3% of patients in the PFHO group and 3.1% in the hypotonic saline group. One patient discontinued PFHO treatment due to a severe ocular AE (ocular irritation), whereas three patients ceased hypotonic saline treatment (conjunctivitis, dry eye, punctate keratitis); no serious ocular AEs were reported in either group. The most commonly reported ocular AEs in patients treated with PFHO, affecting 1% or more, included blurred vision (3.0%; mostly mild and transient) and instillation site pain and eye discharge (both 1.0%). Findings from the GOBI trial underscore the safety, tolerability, and efficacy of PFHO in alleviating signs and symptoms of DED as early as 2 weeks, maintaining through 8 weeks of treatment.

The Mojave study (Sheppard et al., 2023b) aimed to assess NOV03 (perfluorohexyloctane ophthalmic drops) for treating DED linked with MGD. It employed a randomized, double-masked, controlled trial design with patients aged ≥ 18 years. Participants were randomized 1:1 to receive NOV03 or hypotonic saline (0.6%) four times daily for 8 weeks. Primary endpoints included changes in tCFS and eye dryness score (0-100 VAS) from baseline to week 8. Results from 620 patients (NOV03, $n=311$; saline, $n=309$) demonstrated statistically significant improvements favoring NOV03 over saline for tCFS (-2.3 vs -1.1) and dryness score (-29.4 vs -19.2) at week 8. Early differences between groups were evident by week 2. Ocular AEs occurred similarly between NOV03 (12.9%) and

saline (12.3%), with no serious events or discontinuations due to AEs. Conclusively, NOV03 effectively alleviated both signs and symptoms of DED associated with MGD compared to saline, with a favorable safety profile akin to the control.

The KALAHARI trial (Protzko et al., 2023), an extension of the GOBI study, involved patients who had previously participated in either the PFHO or hypotonic saline arms of GOBI. These patients received PFHO four times daily for 52 weeks. Results from KALAHARI supported the long-term effectiveness and safety of PFHO treatment in patients with DED and clinical signs of MGD. After 52 weeks of PFHO treatment, 13.9% of patients experienced ocular AEs, with most being mild in severity. The most common ocular AEs included vitreous detachment (1.9% of patients, none related to treatment), allergic conjunctivitis (1.4%), blurred vision (1.4%), and increased lacrimation (1.4%). Ocular AEs led to treatment discontinuation in 2.4% of patients, including cases of blurred vision, chalazion, dry eye, increased lacrimation, and increased intraocular pressure. Improvements observed in tCFS and VAS dryness scores during the GOBI study among those in the active PFHO arm were sustained throughout the KALAHARI trial. Patients who switched from hypotonic saline to PFHO at the beginning of KALAHARI showed improvement in these measures by week 4, which continued for the duration of the study.

The trial “Perfluorohexyloctane Eye Drops for Dry Eye Disease Associated With Meibomian Gland Dysfunction in Chinese Patients: A Randomized Clinical Trial” (Tian et al., 2023) aimed to assess the efficacy and safety of PFHO eye drops in Chinese patients with DED associated with MGD. Conducted from February 4, 2021, to September 7, 2022 at 15 hospitals in China, the trial included 312 participants. Patients were randomly assigned to receive either PFHO eye drops or 0.6% saline four times daily for 57 days. Results showed that PFHO eye drops significantly improved both the tCFS score and eye dryness score compared to the control group. Specifically, changes from baseline at day 57 in tCFS score (mean [SD], -3.8 [2.7] vs -2.7 [2.8]) and eye dryness score (mean [SD], -38.6 [21.9] vs -28.3 [20.8]) were superior in the PFHO group, with estimated mean differences of -1.14 (95% CI, -1.70 to -0.57 ; $P < .001$) and -12.74 (95% CI, -17.20 to -8.28 ; $P < .001$), respectively. These improvements were noted as early as day 15 and day 29, respectively, and were sustained through day 57. In addition to the primary endpoints, PFHO eye drops also significantly alleviated symptoms such as pain, awareness of DED symptoms, and frequency of dryness compared to the control. Treatment-emergent AEs occurred in 21.8% of

the PFHO group and 25.6% of the control group, with no serious AEs related to the study drug reported. Participant satisfaction and compliance were high in both groups, with a greater satisfaction score reported in the PFHO group (8.4 [1.6] vs 7.5 [2.0]; $P < .001$).

Study “A Review of the First Anti-Evaporative Prescription Treatment for Dry Eye Disease: Perfluorohexyloctane Ophthalmic Solution” (Sheppard et al., 2023a) shows results from multiple clinical trials the consistent efficacy and favorable safety profile of PFHO in treating the signs and symptoms of disease in patients with DED and clinical signs of MGD. PFHO recently received FDA (The United States Food and Drug Administration) approval for treatment of the signs and symptoms of DED, and it may address unmet needs in the prescription treatment of DED. Excessive evaporation is a major contributor to disease pathogenesis and the continuing cycle of DED progression. There are estimated to be over 18 million patients in the United States with a DED diagnosis, most of whom experience excess tear evaporation. PFHO is the first and only FDA-approved prescription eye drop that directly targets excessive evaporation in patients with DED, thereby promoting ocular surface healing and symptomatic relief.

These studies collectively support the efficacy of Miebo® in enhancing tear film stability, alleviating symptoms of DED, particularly in patients with MGD, and establish its role as a valuable therapeutic option in DED management.

Conclusion

In conclusion, Miebo® has demonstrated significant efficacy in improving tear film stability and alleviating symptoms of DED, particularly in patients with MGD. Through a comprehensive review of current clinical evidence, including randomized controlled trials and systematic reviews, Miebo® has consistently shown superiority over traditional treatments like artificial tears and lipid-based formulations.

Clinical trials such as the SEECASE study (Tauber et al., 2021) and the GOBI trial (Tauber et al., 2023) underscored Miebo's effectiveness in reducing tCFS and improving VAS scores for dryness compared to saline controls. Moreover, long-term studies like the KALAHARI trial (Protzko et al., 2023) supported the sustained efficacy and safety of Miebo® over extended treatment periods.

While Miebo® presents a promising therapeutic option for managing DED, ongoing research is crucial to validate its long-term benefits and safety profile. Future studies should focus on addressing gaps in understanding, including optimal dosing regimens and potential interactions with other ocular medications.

In summary, Miebo® represents a significant advancement in the treatment landscape for DED, offering patients a well-tolerated and effective alternative to conventional therapies. Clinicians should consider Miebo® as a valuable addition to their armamentarium in combating the multifaceted challenges of DED.

Authors' Contributions:

Conceptualization was done by Patrycja Nowoświat and Michał Bado; methodology by Michał Andrzej Kozicz; software by Krzysztof Bilecki; checking by Hubert Gugulski, Paulina Cuper, Patrycja Mrowczyk; formal analysis by Ilona Jastrzębska; investigation by Patrycja Nowoświat; resources by Michał Bado; data curation by Krzysztof Bilecki; writing - rough preparation by Patrycja Nowoświat; writing - review and editing by Michał Andrzej Kozicz, Patrycja Mrowczyk; visualization by Ilona Jastrzębska; supervision by Hubert Gugulski; project administration by Paulina Cuper; and receiving funding by Patrycja Nowoświat.

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