

## Perfluorohexyloctane - A Promising Newcomer in Medical Science: A Systematic Review

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### ABSTRACT

**INTRODUCTION:** The new preservative-free treatment for dry eye patients, perfluorohexyloctane, has been considered in recent studies. This study aimed to assess the feasibility of perfluorohexyloctane for dry eye treatment.

**METHODS:** This review was conducted following the PRISMA guidelines. We performed a comprehensive literature search across five online databases: PubMed, Cochrane, ProQuest, ScienceDirect, and Google Scholar. Human studies using perfluorohexyloctane as dry eye or dry eye disease (DED) therapy published in English, and full-text journals available were inclusion criteria in this review. We identified corneal fluorescein staining (CFS) as the main outcome measurement.

**RESULTS:** Five RCTs and two cohort studies were analyzed. Most studies were conducted in Western countries, except one RCT in China. One hundred percent perfluorohexyloctane was used in all studies. All studies showed improvement in CFS to the control group, with a significance level of  $p \leq 0.001$ , except for one study where  $p = 0.2786$ .

**CONCLUSION:** Perfluorohexyloctane shows promising potential as a new therapeutic approach for patients with dry eye disease, but additional research is needed, especially in Eastern countries.

**Keywords:** Dry eye disease, meibomian gland dysfunction, dry eye treatment, perfluorohexyloctane, eye drops, systematic review.

### INTRODUCTION

Dry eye is an ocular condition that has a major impact on the quality of life of millions of people worldwide due to eye discomfort such as burning, itching, redness, gritty feeling, pain, eye fatigue, and visual disturbances [1,2]. It can result from a variety of factors involving the ocular surface. Tear film instability, tear deficiency, excessive

tear evaporation or damage, inflammation of the ocular surface, and neurosensory abnormalities are factors that often cause dry eye [1,3]. The prevalence of dry eye can reach between 5–50% worldwide and 20–52.4%, especially in Southeast Asia. Dry eye is also more common in women compared to men and individuals over 50 years of age [1,4].

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Dry eye often presents a significant challenge for clinicians in providing optimal management to restore comfort for patients. Current therapeutic options include non-lipid and lipid-based eye drops [5]. Lipid-based eye drops are demonstrated to be more efficacious in reducing tear evaporation due to their hydrophobic nature, serving as a prophylactic, particularly under environmental conditions that exacerbate dry eye [3,5]. Despite the availability of these treatments, there remains a demand for more effective therapeutic agents to mitigate symptoms and enhance the quality of life for patients with dry eye.

Perfluorohexyloctane is a synthetic compound with high lipid affinity, is physiologically inert, and has good tolerance for the ocular surface [2,5]. It is also non-aqueous, excelling without the need for preservatives or other fluid additives that may potentially irritate the eye [5]. Along with ongoing developments and advances in ophthalmology, perfluorohexyloctane (F6H8) has recently emerged as an FDA-approved treatment option for dry eye disease [2]. Prior to FDA approval, perfluorohexyloctane had been used in Germany, Austria, Australia, and New Zealand, but not in Asia. Therefore, we conducted a systematic review aimed at evaluating the effectiveness and safety of perfluorohexyloctane as a new preservative-free treatment for dry eye, enabling evidence-based decision-making and guiding future research directions.

## METHODS

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. A comprehensive literature search was performed on five online databases, namely PubMed, Cochrane, ProQuest, ScienceDirect, and Google Scholar. Three independent reviewers conducted the search, and the keywords used were “dry eye disease,” “perfluorohexyloctane,” “dry eye,” “dry eyes,” and their MeSH terms as search keywords. The inclusion criteria for studies were: (1) human studies, and (2) use of perfluorohexyloctane eye drops as therapy for dry eye or dry eye disease (DED). The exclusion criteria were: (1) studies not written in English, (2) full publication was unavailable, and (3) reviews.

The search was conducted up to August 8, 2023. Rayyan, an online-based tool, was used to conduct the screening process [7]. Blinding was maintained until each reviewer completed the screening process, and any disagreements were resolved by discussion. Corneal fluorescein staining (CFS) was analyzed across all included studies. The following data were extracted from each study: authors, year of publication, design, country, number of samples, patient demographics, intervention given, comparison, and CFS outcome.

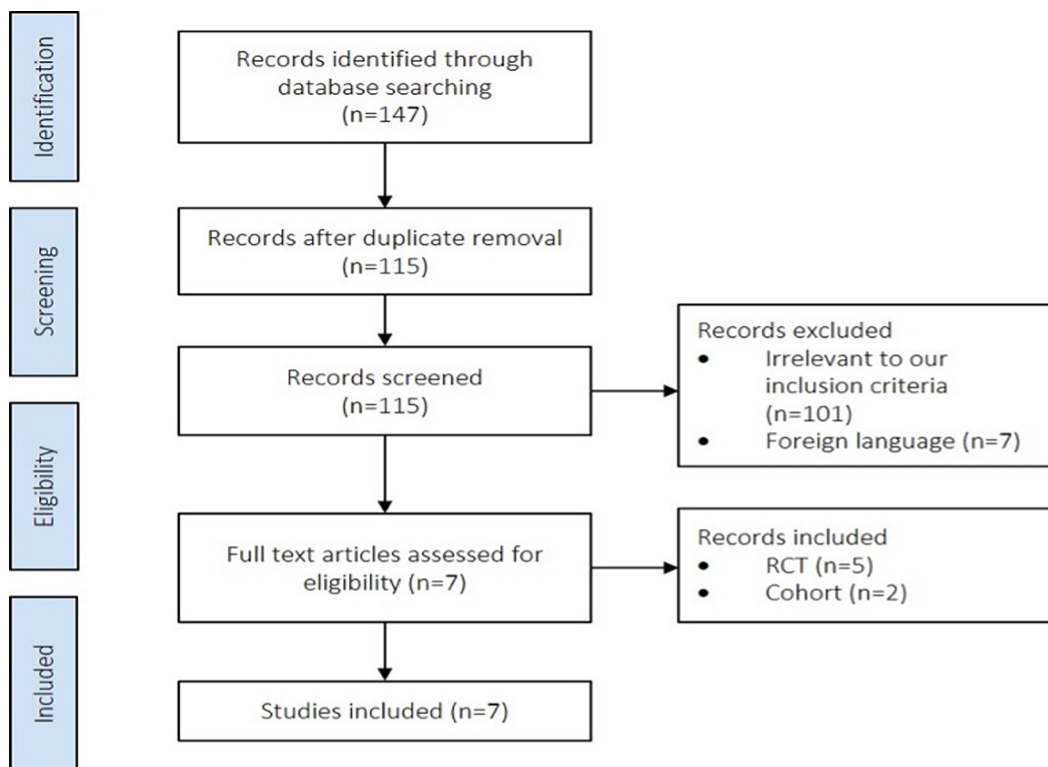
The risk of bias was assessed by three independent reviewers utilizing version 2 of the Cochrane risk of bias assessment tool (RoB 2) for the randomized controlled trials (RCTs) featured in this review [8]. The Newcastle-Ottawa Scale was employed to assess the quality of the cohort studies [9]. Each reviewer carried out the assessments and data extraction independently.

## RESULTS

A total of 147 articles were identified through database searching. Thirty-two articles were removed as duplicates. Of the remaining 115 articles, 7 were excluded due to being in a foreign language (4 in German, 2 in Spanish, and 1 in Russian), and 101 were excluded for not meeting our inclusion criteria. Seven articles were included in this review: 5 RCTs and 2 cohort studies (Figure 1).

Seven studies, involving a total of 2015 participants were analyzed, as shown in Table 1. All participants in this review were adults aged  $\geq 18$  years, with a mean age of 53.31 years. Most of the participants were women. Most studies were conducted in Western countries, except for one RCT in China [12]. Most of the studies involved patients with DED associated with meibomian gland dysfunction (MGD), except for those by Schmidl D. et al. [14] and Steven P et al. [15]. They studied DED patients regardless of whether their condition was associated with MGD or not.

One hundred percent perfluorohexyloctane was used in all studies. In the RCTs, hypotonic saline 0.6% was used as a comparator in three studies [10-12], and isotonic saline 0.9% was used in two studies [13,14]. All studies administered perfluorohexyloctane four times daily (QID). A



**Figure 1: PRISMA flow diagram**

study by Tauber J et al. [11] divided their treatment arms into four groups: perfluorohexyloctane QID, perfluorohexyloctane twice daily (BID), 0.6% sodium chloride QID, and 0.6% sodium chloride BID. In this review, we used their perfluorohexyloctane QID treatment arm results. Most studies had an 8-week follow-up period, except for Schmidl et al. [14] and Steven P et al. [15], which had follow-up periods of 4 weeks and 6 weeks, respectively. All RCT studies used one eye as the outcome measure. The eye with the higher baseline total CFS (tCFS) score was selected. If the baseline tCFS scores were the same in both eyes, the right eye was selected. Besides tCFS, in the study by Schmidl D et al. [14], they chose the study eye with the lower tear film break-up time (TFBUT) at the screening visit first, and when both eyes had identical TFBUT, they chose the eye with the higher tCFS. All cohort studies used both eyes as research subjects, but we only included the right eye in this review.

Also, as shown by Table 1, all studies showed improvement in CFS compared to the control group, with a significance level of  $p \leq 0.001$ , except for one study where  $p = 0.2786$  [14]. The study

by Steven P et al. [15] used the Oxford Grading Scheme to measure CFS. Among the RCT studies, the study by Sheppard JD et al. [10] showed the most significant difference in the CFS outcome. All studies indicated minimal or no serious adverse events. Reported ocular adverse events included blurred vision, eye irritation, eye pain, foreign body sensation, and eye discharge. Four patients in cohort studies showed signs of hypersensitivity to perfluorohexyloctane, which were mild to moderate in intensity but fully recovered thereafter.

The critical appraisal results for each study, based on their respective designs, are presented in Table 2 and 3. Table 2 shows the assessment results for RCTs, all of which indicated a 'low risk' of bias, while Table 3 presents the quality assessment outcomes for the cohort studies. All cohort studies achieved high scores, totaling 9, indicating good quality.

## DISCUSSION

Dry eye disease is a multifactorial condition classified into aqueous-deficient, evaporative, or a combination of the two. Aqueous-deficient DED,

**Table 1: Included studies**

| Author and Year               | Country       | Study Design | Samples | Intervention | Comparison           | CFS Outcome                          |            | p      |
|-------------------------------|---------------|--------------|---------|--------------|----------------------|--------------------------------------|------------|--------|
|                               |               |              |         |              |                      | Intervention                         | Comparison |        |
| Sheppard JD et al., 2023 [10] | United States | RCT          | 620     | 100% PH      | 0,6% Sodium Chloride | -2.3                                 | -1.1       | 0.001  |
| Tauber J et al., 2023 [11]    | United States | RCT          | 597     | 100% PH      | 0,6% Sodium Chloride | -2.0                                 | -1.0       | 0.001  |
| Tian L et al., 2023 [12]      | China         | RCT          | 312     | 100% PH      | 0,6% Sodium Chloride | -3.8                                 | -2.7       | 0.001  |
| Tauber J et al., 2021 [13]    | United States | RCT          | 336     | 100% PH      | Saline solution      | -2.11                                | -0.93      | 0.001  |
| Schmidl D et al., 2020 [14]   | Austria       | RCT          | 48      | 100% PH      | 0,9% Sodium Chloride | -2.8                                 | -3.0       | 0.2786 |
| Steven P et al., 2017 [2]     | Germany       | Cohort       | 72      | 100% PH      | -                    | -0.93                                | -          | 0.0001 |
| Steven P et al., 2015 [15]    | Germany       | Cohort       | 30      | 100% PH      | -                    | 16% reduction from moderate to mild* | -          | 0.0013 |

CFS, corneal fluorescein staining; RCT, randomized controlled trial; PH, perfluorohexyloctane.

\*The study used the Oxford Grading Scheme to measure the CFS.

**Table 2: Risk of bias assessment using RoB 2.0 for RCT studies**

| No | Author and Year               | Domain 1  | Domain 2   | Domain 3               | Domain 4                                     | Domain 5   |
|----|-------------------------------|---|--|------------------------|--|--|
|    |                               | (Risk of bias arising from the randomization process) | (Risk of bias due to deviations from the intended interventions) | (Missing outcome data) | (Risk of bias in measurement of the outcome) | (Risk of bias in selection of the reported result) |
| 1  | Sheppard JD et al., 2023 [10] | Low risk  | Low risk   | Low risk               | Low risk                                     | Low risk   |
| 2  | Tauber J et al., 2023 [11]    | Low risk  | Low risk   | Low risk               | Low Risk                                     | Low risk   |
| 3  | Tian L et al., 2023 [12]      | Low risk  | Low risk   | Low risk               | Low risk                                     | Low risk   |
| 4  | Tauber J et al., 2021 [13]    | Low risk  | Low risk   | Low risk               | Low risk                                     | Low risk   |
| 5  | Schmidl D et al., 2020 [14]   | Low risk  | Low risk   | Low risk               | Low risk                                     | Low risk   |

**Table 3: Quality assessment using the Newcastle-Ottawa Scale for cohort studies**

| No | Author and Year            | Selection                                |                                     |                           | Comparability  |  |                       | Outcome   |                               |   | Overall Quality     |
|----|----------------------------|--|-------------------------------------|---------------------------|--|--|-----------------------|---|-------------------------------|---|---------------------|
|    |                            | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome not present at the start of study | Comparability of cohorts based on the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up cohorts |   |                     |
| 1  | Steven P et al., 2017 [2]  | ★  | ★                                   | ★                         | ★  | ★★   | ★                     | ★   | ★                             | ★ | 9<br>(Good Quality) |
| 2  | Steven P et al., 2015 [15] | ★  | ★                                   | ★                         | ★  | ★★   | ★                     | ★   | ★                             | ★ | 9<br>(Good Quality) |

which affects 10-15% of patients, is characterized by reduced lacrimal gland secretions. In contrast, evaporative DED, accounting for the majority of cases, results from excessive tear film evaporation [10]. DED is more common in females than in males [16-19]. This review consistently found a higher proportion of female participants compared to males. Although the definitive cause remains unclear, some researchers suspect hormonal differences may contribute, as both genders share similar ocular components [16-18]. Besides gender, age is recognized as a factor influencing dry eyes, aligning with our review's finding of a mean age of 53.31 years. Aging correlates with hormonal changes and significant alterations in the quality and lipid profiles of meibomian gland secretions, alongside various age-related factors [16-19].

The primary cause of evaporative DED is MGD, with over 80% of DED patients having meibomian gland involvement [2,10,14]. Alterations in meibum quality or reduced secretion disrupt the tear film lipid layer, causing excessive evaporation and instability. This leads to tear film thinning, desiccation, hyperosmolarity, apoptosis, and ocular surface inflammation, contributing to DED signs and symptoms [10]. Evaporative DED can be associated with several systemic diseases, including atopy, acne rosacea, seborrheic dermatitis, and cicatricial pemphigoid, along with aging processes and drug side effects. Ocular surface inflammation, including eyelid inflammation, plays a central role in the development and persistence of DED. The specific role of inflammation in MGD, however, remains under discussion [2]. All articles in this review also identify MGD as the most common cause of evaporative DED. Two articles by Steven P et al. [2,15] begin by examining the overall causes of DED, then narrow down to MGD as the primary cause. The other five articles directly address MGD as the main cause of DED, along with its pathophysiology, which further clarifies the mechanism of action of perfluorohexyloctane. Based on these seven articles, no studies have yet explored evaporative DED associated with systemic diseases, such as atopy or seborrheic dermatitis, in relation to the effectiveness of perfluorohexyloctane therapy.

Traditional therapies for DED associated with MGD encompass various approaches. Physical treatments, such as lid margin hygiene,

debridement, gland expression, warm compresses, thermal pulsation, and intense pulsed light, aim to enhance meibomian gland secretions [11,15]. Oral medications like doxycycline and azithromycin reduce inflammation or decrease meibum viscosity, while supplements like omega-3 fatty acids complement deficient lipid components from dysfunctional glands [2]. Over-the-counter lipid-based artificial tears, containing oils like castor and mineral oil or stabilizing agents such as polyethylene glycol, temporarily replenish the tear film lipid layer and stabilize the tear film, as shown in clinical trials [11]. However, these stabilizing agents or preservatives can cause inflammation, decreased tear film stability, and reduced therapeutic effectiveness [15]. In this review, we observed that the articles we analyzed collectively indicate that there is currently no specific therapy for DED associated with MGD. While these treatments aim to address DED according to its underlying causes, breakthroughs in topical therapies for DED are either not widely known or not available in many countries, including perfluorohexyloctane.

Perfluorohexyloctane ophthalmic solution offers notable advantages over traditional demulcents or emollients for evaporative dry eye patients. Its amphiphilic properties and low surface tension allow it to spread rapidly across the ocular surface, forming a long-lasting protective layer that prevents tear film evaporation and reduces blinking-related shearing forces [2,10-12,14,15]. This layer remains in tears for up to 6 hours and in meibomian glands for up to 24 hours, with no detectable systemic absorption after a single ocular instillation in rabbits [10]. Additionally, its lipid-dissolving properties help dissolve thickened meibum, reopening gland orifices non-mechanically [2,15]. As a one-component, nonaqueous liquid, it does not support bacterial growth and requires no preservatives, causing minimal visual disturbances due to its refractive index similar to water [10,14]. Perfluorohexyloctane eye drops evaluated in our reviewed articles contain 100% perfluorohexyloctane. Among the five RCT articles, three used 0.6% NaCl as a comparator, while the other used 0.9% NaCl. The use of hypotonic 0.6% NaCl, recommended by the FDA, aims to reduce the hyperosmolarity of the tear film often associated with DED, thereby offering therapeutic benefits for DED [11,12].

The efficacy and safety of perfluorohexyloctane

were confirmed in phase 2 (SEECASE) and phase 3 (GOBI) RCT for DED associated with MGD [11,15]. These studies demonstrated significantly greater reductions in DED signs and symptoms compared to isotonic saline, with a favorable safety profile. In vitro studies of NOV03, one of the commercial formulations for perfluorohexyloctane, showed an 80% reduction in saline evaporation, indicating its effectiveness in preventing tear film evaporation. Perfluorohexyloctane also increased TF BUT, reduced patient symptoms, increased tear volume (measured by the Schirmer test), and reduced ocular surface damage, as shown by fluorescein staining [11]. The evaluation of perfluorohexyloctane's effectiveness varied across the articles. Some studies, such as Sheppard JD et al. [10] and Tauber J et al. [11], have conducted comprehensive assessments, which include CFS, TF BUT, Schirmer's test, best-corrected visual acuity, and clinical signs. In our review, we observed that routine use of perfluorohexyloctane, rarely results in significant adverse effects. Tauber J et al. [11] reported only 1 out of 330 subjects experienced serious eye irritation. Steven P et al. [15] noted that 21 out of 30 subjects intended to continue using perfluorohexyloctane after the study ended. These findings support the benefits of preservative-free, amphiphilic perfluorohexyloctane. However, no articles detailed the storage and stability of preservative-free perfluorohexyloctane. Improper storage may affect its effectiveness in treating DED, considering home use by subjects until follow-up.

Our study has several limitations. First, there is still limited research available on perfluorohexyloctane. Second, existing studies are predominantly conducted in America and Europe. Lastly, most research has concentrated on patients with DED due to MGD, requiring additional research to comprehensively evaluate the therapeutic efficacy of perfluorohexyloctane in evaporative DED patients other than those with MGD.

## CONCLUSION

Perfluorohexyloctane shows promising potential as a new therapeutic approach for patients with evaporative DED, particularly due to MGD. Further large and well-designed RCTs are needed, especially in Eastern countries, to investigate perfluorohexyloctane's efficacy for other causes of evaporative DED beyond MGD.

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