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Efficacy of Perfluorohexyloctane for the Treatment of Patients with Dry Eye Disease: A Meta-Analysis

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Keywords
Perfluorohexyloctane · NOV03 · NovaTears · Dry eye · Ocular surface

Abstract

Introduction: The aim of the study was to systematically review the evidence from randomized controlled trials that evaluate the efficacy and safety of perfluorohexyloctane in the treatment of dry eye disease. ***Methods:*** Literature search was conducted on PubMed and Scopus in April 2024 with the search strategy ("perfluorohexyloctane" or "NOV03" or "semifluorinated alkane") and "dry eye." Extension and paired-eyes study were excluded. The risk of bias was assessed using the Cochrane risk-of-bias tool. Forest plots and a summary of findings were prepared for total corneal fluorescein staining (tCFS), tear film break-up time (TFBUT), eye dryness score (EDS), and Ocular Surface Disease Index (OSDI). ***Results:*** The pooled standardized mean difference (SMD) for tCFS after 8 weeks of treatment was −0.53 (95% CI: −0.68 to −0.38; $p < 0.001$), indicating a significant improvement in patients treated with perfluorohexyloctane. The between-study heterogeneity was moderately high (I^2 = 52.0%). No significant differences in TFBUT were observed (SMD = 0.05; 95% CI: −0.16 to 0.25; $p = 0.654$). Regarding symptoms, patients treated with NOV03 had significantly lower EDS compared to controls (SMD = −0.49; 95% CI: −0.66 to −0.32; $p < 0.001$), with moderately high heterogeneity ($I^2 = 71.1\%$). Conversely, the pooled SMD of OSDI was −0.13 (95% CI: −0.43 to 0.17; $p = 0.412$), indicating no significant difference. ***Conclusion:*** Perfluorohexyloctane is an effective and safe alternative for the treatment of evaporative dry eye disease due to MGD that can significantly reduce tCFS and eye dryness symptoms. More well-designed non-sponsored randomized clinical trials are required to investigate the impact on other ocular surface parameters.

Introduction

Dry eye disease (DED) is a very common ophthalmic condition, affecting millions of patients worldwide [1]. It is characterized by a loss of homeostasis of the tear film, which manifests through a variety of symptoms including

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ocular discomfort and visual disturbance. DED can be caused by both aqueous deficiency and evaporative loss of the tear film, determining a vicious cycle of hyperosmolarity, tear film instability, and ocular surface inflammation [2, 3]. Traditional management strategies for DED range from artificial tear substitutes to more advanced therapeutic interventions, such as nano-based drug delivery systems for eye drops [4–7]. However, the variability in patient response underlines the unmet need for more effective and diverse therapeutic agents. Recent therapeutic strategies for DED have focused on new compounds to mitigate evaporation rate.

Perfluorohexyloctane is an inert semifluorinated alkane which has emerged as a novel agent and was recently approved in Europe as a medical device for the treatment of DED [8]. This fully saturated, linear molecule is characterized by a hydrogenated carbon chain, which confers hydrophobic properties to the compound [9]. Perfluorohexyloctane has multiple mechanisms of action. Primarily, it replaces the defective tear film lipid layer while forming a protective overlay at the tear film-air interface, significantly reducing evaporation rate [10–12]. The structural properties of the hydrocarbon chains in meibum lipids play a crucial role in maintaining tear film stability. The degree of unsaturation of these chains determines the fluidity and spreading of the lipid layer on the ocular surface. Less unsaturated lipids are stiffer, which increases lipid clumping, eventually obstructing meibomian glands [13, 14]. Perfluorohexyloctane improves the structure of the lipid layer, stabilizing the tear film and reducing DED symptoms [15]. Finally, perfluorohexyloctane shows oxygen-carrying capacity, allowing the delivery of non-reactive oxygen species to the cornea, which is critical for the health of the ocular surface [16].

These properties make perfluorohexyloctane a compelling candidate for addressing the evaporative component of DED [17]. Randomized controlled trials (RCTs) have suggested the efficacy of perfluorohexyloctane in ameliorating signs and symptoms in patients affected by evaporative DED [18–22]. The purpose of this meta-analysis is to systematically review the evidence from RCTs that evaluate the efficacy and safety of perfluorohexyloctane in the treatment of DED.

Methods

Study Selection

Comprehensive literature search was conducted by two authors (A.T. and M.P.) on PubMed and Scopus in April 2024. The website clinicaltrials.gov was queried to identify ongoing unpublished RCTs. The search strategy used was ("perfluorohexyloctane" or "NOV03" or "semifluorinated alkane") and "dry eye." The analysis of the literature was performed according to the PRISMA guidelines. After removing duplicates, titles and abstracts were evaluated. Relevant articles were subjected to full-text examination. References of all the full texts were manually checked for additional related studies. Included studies were limited to RCTs involving adult human subjects affected by DED. Only English-written articles were included. Extension studies, trials involving less than 30 eyes, and/or paired eyes were excluded.

Bias Assessment

The risk of bias for each RCT was assessed by two authors (A.T. and M.P.) using the Cochrane risk-of-bias tool [23]. Five domains were evaluated: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported results. Disagreements were resolved by discussion and consensus with a third author (G.G.). Each domain was classified as "low risk," "some concerns," "high risk."

Data Extraction

Data extraction was independently performed by two authors (A.T. and M.P.), using a standardized form. From each RCT, results about the following study variables with 2-, 4-, 8-week follow-ups (FUs) were recorded: (1) total corneal fluorescein staining (tCFS), (2) tear film break-up time (TFBUT), (3) eye dryness score (EDS) assessed by a visual analogue scale (VAS), (4) ocular burning/stinging assessed by VAS scale, (5) Ocular Surface Disease Index (OSDI), (6) unanesthetized Schirmer test (ST), and (7) meibomian gland dysfunction (MGD) score. In case of missing data, the principal investigators of the RCTs were emailed to request access to the original data sets. The meta-analysis was conducted using the available information when no response was received within a 4-week period.

Statistical Analysis

Forest plot analyses were performed for the following outcomes: tCFS, TFBUT, EDS, and OSDI. Results were reported as mean ± standard deviation. For continuous variables, mean differences (MDs) and standardized mean differences (SMD) with 95% confidence intervals (CIs) and p values were calculated. A random-effects model was used by default to perform

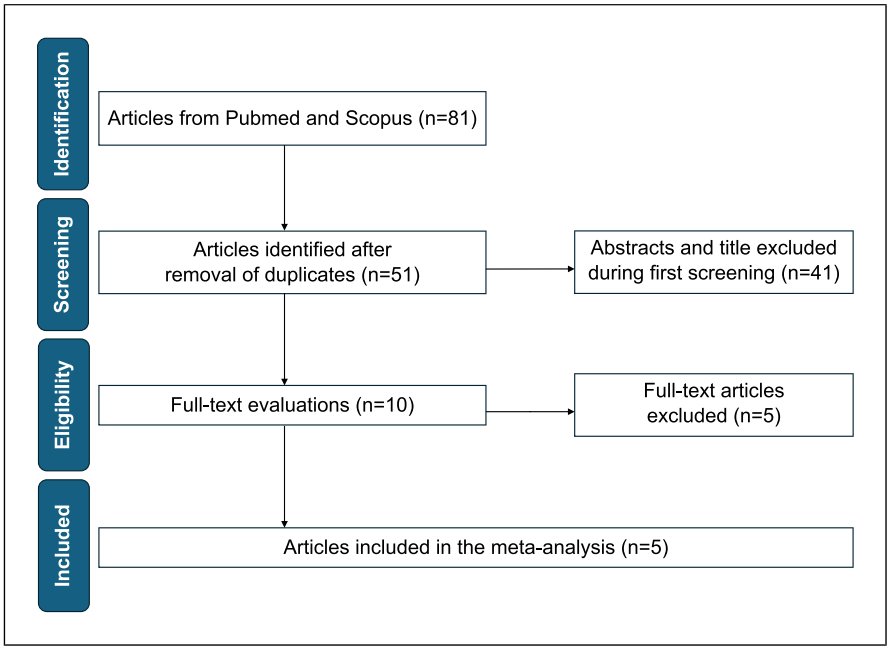

Fig. 1. PRISMA flowchart for the article selection process.

the meta-analysis. For TFBUT, the DerSimonian and Laird estimator (τ) was negative; therefore, a random-effects model could not be applied, and a fixed-effects model was used instead. Heterogeneity values were calculated. The quality of evidence for each outcome was graded according to the GRADE classification system in "very low," "low," "moderate," or "high." The incidence of ocular treatment-emergent adverse events (TEAEs) was reported and analyzed as relative effect (95% CI). A "Summary of Findings" table was prepared for all outcomes.

A p value <0.05 was considered statistically significant (two-sided test). Sensitivity and subgroup analyses were not performed due to the small number of RCTs involved in the meta-analysis. All data were entered into an electronic database via Microsoft Office Excel 365 (Microsoft Corp., Redmond, WA, USA) and analyzed with IBM SPSS Statistics (version 29.0; IBM, Armonk, NY, USA). Forest plots were created using R.

Results

Results of Search

A total of 81 articles were retrieved in the literature search. After removing duplicates (n = 30), 51 abstracts were screened. After excluding unrelated items, full-text examination was conducted on 10 articles. One study was excluded because it investigated severe dry eye cases due to graft-versus-host disease [24], 2 because they were extension studies [25, 26], 1 because it reported data for paired eyes, which could lead to intra-subject correlation [10], and 1 because of the comparative design with a non-control cohort [27]. Overall, 5 RCTs were included in the meta-analysis (one phase 2 studies, three phase 3 studies, and one phase 4 studies) (shown in Fig. 1).

Study design and inclusion criteria for each RCT are reported in Table 1. In all studies, the investigated intervention was the instillation of perfluorohexyloctane eye drops administered 4 times daily. Four RCTs used the NOV03 formulation (Novaliq GmbH, Heidelberg, Germany), while Schmidl et al. [18] used NovaTears (Novaliq GmbH, Heidelberg, Germany). For comparison, patients instilled a sodium chloride solution (either 0.6 or 0.9%) 4 times daily. All RCTs were multicentric, double-masked, with an 8-week FU, except for the study by Schmidl et al. [18], which was conducted in a single site (Austria, Vienna), was single-masked, and had a FU period of 4 weeks. Inclusion criteria were identical in the 4 multicentric studies (TFBUT ≤5 s; ST I ≥5; OSDI ≥25; tCFS ≥4, ≤11; MGD score ≥3), while the criteria for the study by Schmidl et al. [18] were less strict.

Risk of Bias

A risk-of-bias summary is shown in Figure 2. Randomization was computer-based and provided by the sponsor in the study by Schmidl et al. [18]; in

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Table 1. Study design, inclusion criteria, and demographic data for the RCTs included in the meta-analysis

RCT (first author, study name, clinical trial identifier, year)	FU, weeks	Setting	Patients (intervention/ comparison)	Sex, M (%)/ F (%)	Age, mean±SD, years	Intervention	Comparison	Inclusion criteria						
								history of DED, months	TFBUT, s	ST, mm	OSDI, score	tCFS, score	MGD, score	VAS for DED symptoms, score
Schmidl et al. [18] (2020), NCT03048526	4	Single site (Austria, Vienna), phase 4, single-masked (observer-blinded)	48 (24/24)	12 (75%)/ 36 (25%)	37.5±12.5	(NovaTears) perfluorohexyloctane, 4 times daily	Unpreserved 0.9% sodium chloride, 4 times daily	≥3	≤10	≥5, ≤15	–	–	–	≥20, ≤70
Sheppard et al. [19] (2023), MOJAVE, NCT04567329	8	42 sites (USA), phase 3, double-masked	620 (311/309)	132 (21.3%)/ 488 (78.7%)	53.5±20.3	(NOV03) perfluorohexyloctane, 4 times daily	0.6% sodium chloride, preserved with 0.01% BAK, 4 times daily	≥6	≤5	≥5	≥25	≥4, ≤11	≥3	–
Tauber et al. [20] (2021), SEECASE, NCT03333057	8	12 sites (USA), phase 2, double-masked	225 (114/111)	66 (29.3%)/ 159 (70.7%)	53.6±19.9	(NOV03) perfluorohexyloctane, 4 times daily and 2 times daily	0.9% sodium chloride, 4 times daily and 2 times daily	–	≤5	≥5	≥25	≥4, ≤11	≥3	–
Tauber et al. [21] (2023), GOBI, NCT04139798	8	26 sites (USA), phase 3, double-masked	597 (303/294)	164 (27.5%)/ 433 (72.5%)	60.9	(NOV03) perfluorohexyloctane, 4 times daily	0.6% sodium chloride, preserved with 0.01% BAK, 4 times daily	≥6	≤5	≥5	≥25	≥4, ≤11	≥3	–
Tian et al. [22] (2023), NCT05515471	8	15 sites (China), phase 3, double-masked	312 (156/156)	67 (21.5%)/ 245 (78.5%)	44.6±15.2	(NOV03) perfluorohexyloctane, 4 times daily	0.6% sodium chloride, 4 times daily	≥6	≤5	≥5	≥25	≥4, ≤11	≥3	–

FU, follow-up; SD, standard deviation; BAK, benzalkonium chloride; DED, dry eye disease; TFBUT, tear film break-up time; ST, Schirmer test; OSDI, Ocular Surface Disease Index; tCFS, total corneal fluorescein staining; MGD, meibomian gland dysfunction; VAS, visual analogue scale.

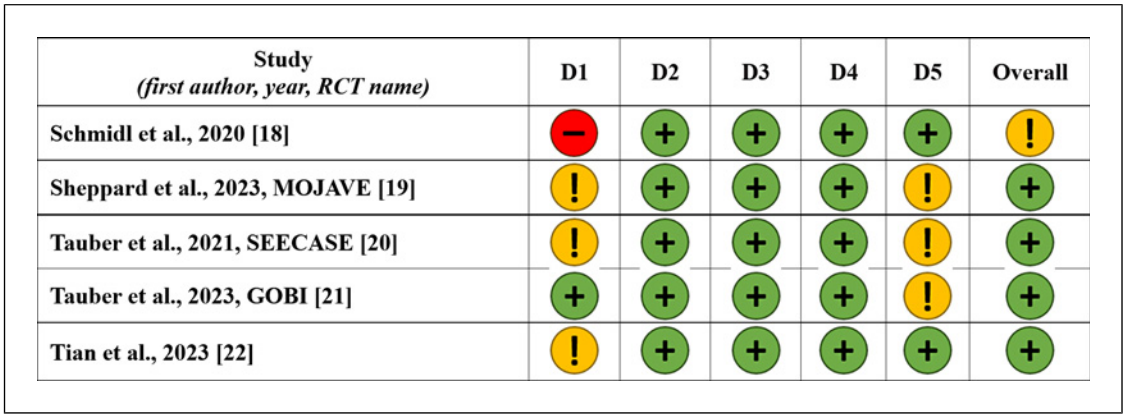

Fig. 2. Risk-of-bias assessment according to the Cochrane risk-of-bias tool. D1, randomization process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result; + = low risk; ! = some concerns; – = high risk. RCT, randomized controlled trial.

Table 2. Summary of findings of the following outcomes: tCFS, TFBUT, EDS as assessed by a VAS, and OSDI score

Outcomes	Mean in intervention group (SD)	Mean in control group (SD)	MD (95% CI)	SMD (95% CI), *p* value	Participants (studies), *n*	Certainty of the evidence (GRADE)[a]
tCFS	4.28 (2.05)	5.38 (2.01)	−1.06 (−1.31, −0.81)	−0.53 (−0.68, −0.38), <0.001	1,802 (5)	⊕⊕⊕⊕ high
TFBUT	4.54 (2.19)	4.45 (2.42)	0.12 (−0.34, 0.59)	0.05 (−0.16, 0.25), 0.654	360 (2)	⊕◯◯◯ very low
EDS VAS	34.51 (17.32)	43.61 (17.81)	−7.22 (−17.25, 2.8)	−0.49 (−0.66, −0.32), <0.001	1,577 (4)	⊕⊕⊕⊕ high
OSDI	36.24 (15.44)	39.28 (15.19)	−1.89 (−9.18, 5.39)	−0.13 (−0.43, 0.18), 0.412	585 (3)	⊕⊕◯◯ low

SD, standard deviation; CI, confidence interval. High: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[b] is low. Moderate: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[b] is moderate. Low: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[b] is high. Very low: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[b] is very high. Perfluorohexyloctane eye drops for the treatment of DED: (a) patients or population: 1,802; 465 (25.8%) M, 1,337 (74.2%) F; mean age 54.02 years; (b) settings: 96 sites (USA, China, Austria); (c) design: one phase 2, three phase 3, and one phase 4 RCTs, double-masked (except Schimdl et al. [18], single-masked); (d) FU: 8 weeks; (e) intervention: perfluorohexyloctane eye drops 4 times daily; (f) comparison: hypotonic saline solution (either 0.6 or 0.9% NaCl) 4 times daily. [a]GRADE working group grades of evidence. [b]Substantially different, a large enough difference that it might affect a decision.

the other RCTs, randomization was centralized across study centers. Stratification was based on clinical site and EDS in the MOJAVE (Sheppard et al. [19]) and GOBI (Tauber et al. [21]) studies. Allocation concealment was not clearly explained in any RCT, except the GOBI study. Participants were not masked in the study by Schmidl et al. [18]. The MOJAVE, SEECASE (Tauber et al. [20]), and GOBI studies included baseline data about TFBUT, ST, and MGD score at baseline, but did not provide the same measurements for the last visit. Additionally, the GOBI study did not report OSDI at the last visit. All studies were sponsored and financed by Novaliq GmbH (Heidelberg, Germany) and Bausch + Lomb (NY, USA). In

Table 3. Baseline, last visit, and CFB for both intervention and control groups of the five included RCTs

RCT (first author, study name, year)	Time point	tCFS (0–15)		TFBUT (s)		EDS VAS (0–100)		OSDI (0–100)		Patients with ≥1, ocular TEAE, *n* (%)	
		study	control	study	control	study	control	study	control	study	control
Schmidl et al. [18] (2020)	Baseline	4.1±1.4	3.8±1.4	3.7±1.7	3.8±2.1	35±15	32±14	44±22	40±14	–	–
	Last visit	2.8±1.6	3.1±1.6	5.1±2.7	5.7±3.1	22.2±17.3	20.2±17.3	33.4±21.6	30.4±21.6	–	–
	CFB	−1.3	−0.7	1.4	1.9	−12.8	−11.8	−10.6	−9.6	–	–
Sheppard et al. [19] (2023), MOJAVE	Baseline	7±2	7.1±2.1	3.2±0.9	3.1±0.9	64.7±19.5	64.3±19.8	55.2±17.4	55.8±17.2	–	–
	Last visit	4.7±1.6	6±1.9	–	–	35.2±15.5	45.3±16.5	31.9	39.9	40 (12.9)	38 (12.3)
	CFB	−2.3	−1.1	–	–	−29.5	−19	−23.3	−15.9	–	–
Tauber et al. [20] (2021), SEECASE	Baseline	7±2.2	6.7±2	3±0.9	3±0.9	68.6±21.8	66.8±21.7	55.3±7.4	54±16.9	–	–
	Last visit	4.89±1.8	5.77±1.8	–	–	37	47.1	51±9.2	51±9.2	13 (11.4)	13 (11.7)
	CFB	−2.11	−0.93	–	–	−31.6	−19.7	−4.3	−3	–	–
Tauber et al. [21] (2023), GOBI	Baseline	6.7±1.8	6.7±1.9	3.2±0.8	3.3±0.8	66.5±19.1	66.8±18.7	53.9±17.6	54.4±17	–	–
	Last visit	4.7±2.2	5.7±2	–	–	39.1±16.4	47.1±17.4	–	–	29 (9.6)	22 (7.5)
	CFB	−2	−1	–	–	−27.4	−19.7	–	–	–	–
Tian et al. [22] (2023)	Baseline	6.2±1.9	6.3±1.7	3±0.9	2.9±0.9	64.7±15.1	65.6±16.5	55.8±16.6	56.2±16.6	–	–
	Last visit	2.4±2.7	3.6±2.4	4.452±2.1	4.263±2.3	26.1±21.9	37.3±20.9	25.9±17.8	32.3±17.3	22 (14.1)	24 (15.4)
	CFB	−3.8	−2.7	1.5	1.4	−38.6	−28.3	−29.9	−23.9	–	–

tCFS, total corneal fluorescein staining; TFBUT, tear film break-up time; EDS, eye dryness score; VAS, visual analogue scale; OSDI, Ocular Surface Disease Index; TEAE, treatment-emergent adverse event.

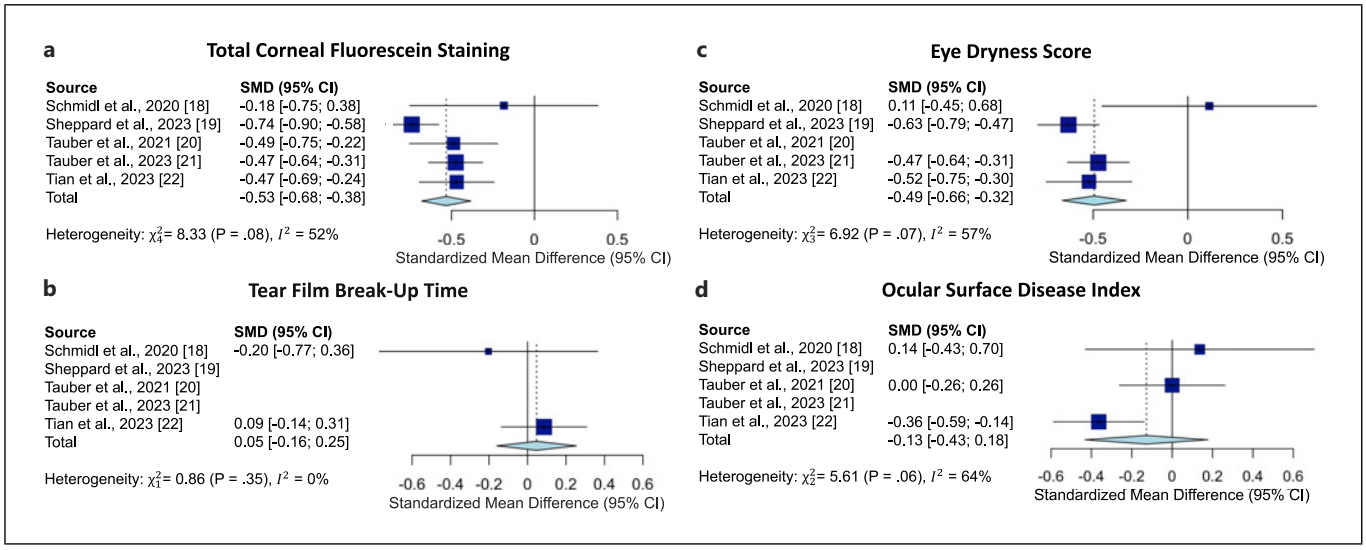

Fig. 3. Forest plots for tCFS (**a**), TFBUT (**b**), EDS (**c**) as assessed by a VAS, and OSDI (**d**). SMD, standardized mean difference; CI, confidence interval.

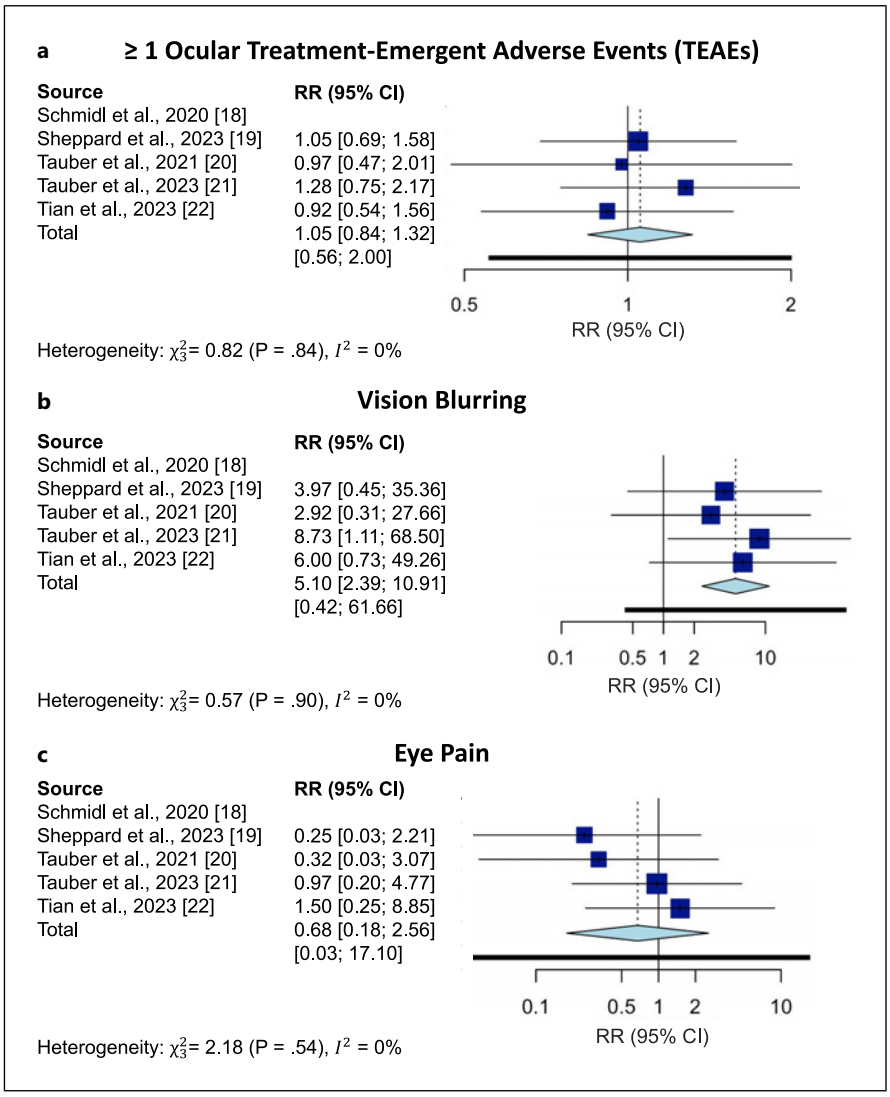

Fig. 4. Forest plots for number of patients with at least ocular TEAEs (**a**), blurred vision (**b**), and eye pain (**c**). RR, relative risk; CI, confidence interval; PI, prediction interval.

summary, the risk of bias was low in all studies, except for the RCT by Schmidl et al. [18], which presented some concerns related to randomization and masking.

Summary of Findings

A summary of findings is shown in Table 2. Overall, 1,802 patients were recruited in 96 different sites (USA, China, Austria) between December 2016 and July 2021. By design, the SEECASE study included two distinct treatment groups: one received perfluorohexyloctane 4 times daily and the other twice daily. For the purpose of the meta-analysis, only results from the group treated 4 times daily were considered. Similarly, the control group also encompassed 2 dosage regimens (twice daily and 4 times daily), but the two subgroups were not divided by the authors. Therefore, it was not possible to differentiate between the 2 dosage subgroups for the purpose of the statistical analysis.

In total, 908 patients were treated with perfluorohexyloctane eye drops 4 times daily, while 894 received a saline solution (either 0.6 or 0.9% NaCl). Most participants were females (F = 1,337; M = 465). Weighted mean age was 54.0 years. The last visit was performed at week 8 in all studies, except in the RCT by Schmidl et al. [18] (week 4). Baseline, last visit, and change from baseline (CFB) for both intervention and control groups of the 5 included RCTs are shown in Table 3.

Total Corneal Fluorescein Staining

A meta-analysis in relation to tCFS was performed for all 5 studies (1,802 patients). The pooled MD of tCFS after treatment was −1.06 (95% CI: −1.31 to −0.81). The pooled SMD was −0.53 (95% CI: −0.68 to −0.38; $p < 0.001$), indicating a significantly lower tCFS in patients treated with perfluorohexyloctane eye drops (shown in Fig. 3a). The between-study heterogeneity was moderately high ($I^2 = 52.0\%$).

Tear Film Break-Up Time

A meta-analysis in relation to TFBUT was performed in 2 out of 5 studies (360 patients), because 3 studies did not include last visit data for this parameter. The pooled MD of TFBUT after treatment was 0.12 (95% CI: −0.34 to 0.59). The pooled SMD was 0.05 (95% CI: −0.16 to 0.25; $p = 0.654$), showing no significant difference between the treatment and control group (shown in Fig. 3b), with a low heterogeneity ($I^2 = 0\%$).

VAS for Eye Dryness

A meta-analysis in relation to EDS was performed in 4 out of 5 studies (1,577 patients), because 1 study did not include sufficient data to analyze this parameter. The pooled MD of the EDS after treatment was −7.22 (95% CI: −17.25 to 2.8). The pooled SMD was −0.49 (95% CI: −0.66 to −0.32; $p < 0.001$), indicating a significantly lower EDS in patients treated with perfluorohexyloctane eye drops (shown in Fig. 3c). A moderate heterogeneity was observed ($I^2 = 56.6\%$).

Ocular Surface Disease Index

A meta-analysis in relation to OSDI score was performed in 3 out of 5 studies (583 patients), because 2 studies did not include sufficient data to analyze this parameter. The pooled MD of the EDS after treatment was −1.89 (95% CI: −9.18 to 5.39). The pooled SMD was −0.13 (95% CI: −0.43 to 0.17; $p = 0.412$), indicating no significant difference between patients treated with perfluorohexyloctane and control subjects, along with a moderately high heterogeneity ($I^2 = 64.4\%$) (shown in Fig. 3d).

Ocular TEAEs

The number and percentage of ocular TEAEs were reported in 4 out of 5 RCTs. Overall, 104 patients (11.7%) in the intervention group and 97 (11.1%) in the control group presented at least 1 ocular TEAE, with a nonsignificant relative risk (RR) of 1.05 (95% CI: 0.84 to 1.32; $p = 0.506$) (shown in Fig. 4a). The most common TEAE was vision blurring, reported by 22 patients (2.5%) of the intervention group and 4 patients (0.5%) in the control group. The RR was statistically significant (RR = 5.10, 95% CI: 2.39 to 10.91; $p = 0.006$) (shown in Fig. 4b). Eye pain was rarer, occurring in 8 patients (0.9%) of the intervention group and 12 patients (1.4%) of the control group (RR = 0.68, 95% CI: 0.18 to 2.56; $p = 0.418$) (shown in Fig. 4c).

Discussion

In this meta-analysis, the efficacy and safety of eye drops based on semifluorinated alkane perfluorohexyloctane (F6H8) have been evaluated across available RCTs. These eye drops only include a lipidic component; therefore, they may be considered as the first water-free eye drops [21]. However, unlike typical lipid-containing eye drops, which are often viscous, perfluorohexyloctane has a refractive index similar to water, minimizing vision blurring [28].

The mechanism of action of perfluorohexyloctane has been extensively investigated. Its efficacy depends on the replenishment and enhancement of the lipid layer of the tear film [15]. Both in vitro and in vivo studies demonstrated that perfluorohexyloctane eye drops reinforce the lipid layer, greatly reducing the evaporation rate of the aqueous layer of the tear film [9, 18]. Such effect is determined by perfluorohexyloctane's hydrophobic structure and low surface tension, allowing for uniform distribution of the eye drops on the ocular surface, and forming a protective layer on top of the defective meibum, at the tear film-air interface [29]. In addition, perfluorohexyloctane has oxygen-carrying capacity, which improves healing in DED patients [16].

Another possible mechanism of action is the biochemical interaction with the meibum. Kroesser et al. [30] demonstrated high affinity of carbon 14-labeled perfluorohexyloctane for the meibomian gland in a rabbit model. After penetrating the gland, perfluorohexyloctane solubilized the pathological, viscous meibum. If demonstrated in humans, these synergistic properties could be especially useful for the treatment of evaporative DED due to MGD.

In the context of evaporative DED, MGD has traditionally been thought to play a key role, predominantly through the mechanism of increased tear film evaporation due to lipid layer insufficiency [31, 32]. However, recent in vitro studies have shown a negligible impact of meibum lipids in inhibiting tears' evaporation rate. As a consequence, this finding raises questions about the impact of the native tear film lipid layer in reducing tear

evaporation in vivo [9]. Furthermore, several authors have found no significant differences in lipid layer thickness (LLT) between patients with and without DED [33–36]. Remarkably, researchers reported that patients affected by evaporative DED with obstructive MGD were found to have higher LLT than those affected by evaporative DED with nonobstructive MGD [37–39]. It should also be noted that LLT measurements can vary widely both among individuals and within the same tear film lipid layer, complicating their interpretation [35, 40–42]. These findings suggest that the relationship between LLT and tear film evaporation may be more complex than previously thought, necessitating further investigation.

Based on our literature search, the results of ten completed RCTs were published. Of these, 5 were included in the meta-analysis [18–20]. Adult patients affected by mild to moderated DED participated in the trials. The FU was 8 weeks in all RCTs, except in the study by Schmidl et al. [18] (4 weeks). In the SEECASE study, Tauber et al. [21] found that the efficacy of perfluorohexyloctane in improving signs and symptoms of DED is dose dependent. Consequently, all subsequent studies adopted a QID dosing schedule (4 times daily) instead of a BID one (twice daily). The MOJAVE, SEECASE, and GOBI studies, as well as the trial by Tian et al. [22], employed the NOV03 formulation (Novaliq GmbH, Heidelberg, Germany). These 4 RCTs were multicentric and double-masked. Instead, the other RCT by Schmidl et al. [18] tested the NovaTears formulation (Novaliq GmbH, Heidelberg, Germany). It was performed in a single site, and only observers were masked. Baseline tCFS, TFBUT, EDS, unanesthetized ST, MGD score, and OSDI were measured in all studies; however, last visit measurements were not always reported for all the variables. The study by Schmidl et al. [18] was the only one to evaluate NITFBUT, LLT, and tear film thickness by the means of optical coherence tomography. However, the sample size was very limited (24 patients for the intervention group).

The meta-analysis was conducted for tCFS, TFBUT, EDS, and OSDI. Last visit data for tCFS were reported by all studies. A significant SMD of −0.53 ($p < 0.001$) was found between intervention and control group, with a medium heterogeneity. This outcome can be attributed to the long-lasting protection of perfluorohexyloctane on the ocular surface (up to 6 h in rabbit models) [15].

It is well known how a physiological lipid layer is essential to stabilize the tear film [43]. Schmidl et al. [18] were the only authors to report data about LLT. The LLT relative CFB was significantly higher for perfluorohexyloctane than for the saline solution at 4 weeks (least squared MD = 16.34%, $p < 0.01$). An increased thickness of the lipid layer has been statistically correlated to higher values of TFBUT and ST score [44]. However, in our meta-analysis, last visit data for TFBUT showed no significant difference between intervention and control group (SMD = 0.05, $p = 0.654$). This unexpected result is probably due to the small sample size and short FU of the studies reporting TFBUT data (2 out of 5).

Tian et al. [22] were the only authors to report MGD score and ST values for last visit. The improvements were comparable between intervention and control groups, for both MGD score (intervention group CFB = −2.1, control group CFB = −1.8; $p = 0.33$) and ST (intervention group CFB = −1.0, control group CFB = 0.3; $p = 0.12$).

Concerning symptoms, EDS data were reported in 4 out of 5 studies. The meta-analysis showed an overall significant reduction of EDS after treatment (SMD = −0.49, $p < 0.001$). OSDI last visit data were available in 3 out of 5 studies. There was no significant difference between intervention and control group (SMD = −0.13, $p = 0.412$); however, a significant effect was found for the study by Tian et al. [22] (SMD = −0.36, $p = 0.001$).

These findings were recently confirmed by the KALAHARI study, a phase 3, multicenter, open-label extension study of the GOBI trial, with a 12-month FU. Both the intervention and control groups of the GOBI study were treated with perfluorohexyloctane. The reductions in tCFS and EDS observed in the GOBI study were sustained throughout the KALAHARI study. The patients who switched from saline solution to perfluorohexyloctane showed significant improvements in DED signs and symptoms compared to baseline [26].

The certainty of the evidence was considered high for the analyses of tCFS and EDS, low for TFBUT and OSDI. In general, perfluorohexyloctane eye drops were well-tolerated, with a low percentage of patients affected by ocular TEAEs (11.7%), mainly blurred vision (2.4%). No severe adverse events related to the treatment were reported.

The main limitation of this meta-analysis was the low quantity of published RCTs. All studies were sponsored, introducing a possible bias. In the MOJAVE, SEECASE, and GOBI studies, outcome selection may be biased, as several baseline variables (TFBUT, OSDI, ST, and MGD score) were not assessed at last visit.

Different sodium chloride solutions were used for the control groups, which may have altered results. In the SEECASE study and in the trial by Schmidl et al. [18], 0.9% saline solution was used. The SEECASE study

included 2 different dosage regimens (twice a day and 4 times a day) for controls, without providing separate results for the 2 subgroups. Conversely, Sheppard et al. [19], Tauber et al. [21], and Tian et al. [22] used a hypotonic 0.6% saline solution. Hypotonic saline solutions are arguably better comparators, as they have been reported to be effective in the treatment of DED. In fact, they reduce the hyperosmolarity of the tear film, which plays a key role in the vicious cycle of DED [22, 45].

Additionally, the perfluorohexyloctane formulations used were preservative-free. This was not always the case for the control saline solutions. Except for Schmidl et al. [18], saline solutions were either preserved with benzalkonium chloride (BAK) or the authors did not provide information about the presence of preservatives. BAK has been clearly associated with ocular surface toxicity [46]. BAK induces an inflammatory response, alters the viability and functionality of meibomian glands, damages corneal epithelial cells, and triggers conjunctival goblet cell apoptosis [47]. Therefore, chronic exposure to BAK may lead to tear film instability, exacerbating the symptoms of DED [48].

In conclusion, the results of this meta-analysis demonstrated a significant effect of perfluorohexyloctane in reducing tCFS and eye dryness symptoms. Perfluorohexyloctane is an effective and safe alternative for the treatment of evaporative DED; however, more well-designed non-sponsored RCTs are required to investigate the impact on TFBUT, MGD score, and ST values.

Statement of Ethics

A statement of ethics and a consent to participate are not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, G.G., G.C., M.P., and A.T.; methodology, G.G., M.P., and V.S.; validation and visualization, G.G., A.T., M.P., G.C., and V.S.; formal analysis and data curation, A.T. and M.P.; investigation, G.G., A.T., M.P., and G.C.; writing – original draft preparation, A.T. and G.C.; writing – review and editing, G.G., and V.S.; supervision, G.G., M.P., and V.S.; project administration, G.G., G.C., and V.S. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Further inquiries can be directed to the corresponding author Giuseppe Giannaccare at giuseppe.giannaccare@unica.it. This study is a meta-analysis, based on publicly available data in: [18–22].

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