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Can the optimum artificial tear treatment for dry eye disease be predicted from presenting signs and symptoms?

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ABSTRACT

Purpose: To assess dry eye treatment with four preservative-free dry eye artificial tear treatments to facilitate evidence-based prescribing.
Methods: A randomised, single masked crossover trial of Clinitas Soothe, Hyabak, Tears Again and TheraTears artificial tears was conducted on 50 symptomatic dry eye patients, aged 60.8 ± 14.2 years. At baseline and after trialling each treatment for 4 weeks, signs and symptoms were assessed using the Ocular Surface Disease Index (OSDI), non-invasive tear break-up time, fluorescein tear break-up time, tear meniscus height (TMH), Phenol Red test, lid-parallel conjunctival folds (LIPCOF), ocular surface staining, and lipid layer grading and osmolarity (baseline visit only).
Results: OSDI ($p = 0.002$), LIPCOF ($p = 0.014$) and conjunctival staining ($p < 0.001$) significantly improved from baseline, however, the impact of each dry eye treatment on ocular symptoms and signs was similar. Clinitas Soothe and Hyabak were preferred by 34%/30% of participants, but only subjective comparison with the other drops influenced this choice. TheraTears was preferred (by 24%) by those with a lower baseline tear volume ($p = 0.01$) and Tears Again (by 12%) by those with a thinner baseline lipid layer ($p = 0.04$). The treatment that afforded the greatest improvement in clinical signs did not consistently match each individual's preferred treatment.
Conclusions: If prescribed to a general dry eye population, the artificial tears performed similarly, improving symptoms and conjunctival signs. However, osmolarity balanced artificial tears were the preferred treatment in individuals with low baseline tear volume and lipisomal spray for individuals with a baseline lipid layer deficiency.

1. Introduction

Dry eye signs and symptoms are typically triggered by a dysfunction of the ocular tear film, which may arise due to deficiencies in the aqueous phase of the tear film (termed aqueous-deficient dry eye) and, more commonly, the lipid phase of the tear film (termed evaporative dry eye) [1]. The primary course of dry eye treatment is topical application of eye drops, gels and sprays to re-build and stabilise the tear film. Numerous compositions of dry eye treatments are commercially available, principally differing in which element of the tear film they primarily aim to replace. Sodium hyaluronate is a glycosaminoglycan with viscoelastic properties [2] that increases tear film stability [2–4] and promotes epithelial cell migration [5,6]. Carboxymethylcellulose (CMC) is an anionic cellulose polymer with a carboxylic group, which exhibits a high affinity for bioadhesion [7], increases tear film stability [3] and promotes epithelial cell migration [8]. Liposomal dry eye treatments consist of phospholipids, which enhance the lipid tear film layer [9] and also increase tear film stability [9–11]. Osmolarity is considered a key driver of ocular surface damage from dry eye [12] and an artificial tear has been formulated to overcome this but this has not been extensively tested clinically against other treatment options [13]. Approximately 78% of dry eye patients have been reported to have lipid layer deficiencies [1], therefore Lee and colleagues recommended liposomal sprays should be the first choice of treatment for all dry eye patients [14]. However previous studies tend to compare the benefit of one 'class' of artificial tear, with perhaps saline as a control, some over short durations, rather than cross class to inform optimum prescribing decisions (Table 1).

Despite knowing that artificial treatment individually helps to reduce symptoms compared to a saline placebo, evidence-based criteria indicating which composition of treatment is best suited to alleviate particular dry eye signs and symptoms are currently unavailable. The

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Table 1
Summary of dry eye studies comparing artificial tears dry eye treatments on patients without Sjögren's syndrome. OSDI = Ocular Surface Disease Index; NITBUT = Non-Invasive Tear Break-Up Time; TBUT = fluorescein Tear Break-Up Time; LLG = Lipid Layer Grade; TMH = Tear Meniscus Height; LIPCOF = Lid Parallel Conjunctival Folds; CD44 = hyaluronate receptor.

Study	Drops Used	Tests compared	Design	Sample Size	Evaluation period	Conclusions
Brignole et al. [15]	• Sodium hyaluronate (0.18%) • CMC (1%)	• Flow cytometry • Subjective reports	Randomised, double-masked, non-crossover study	22 (100% documented history of moderate dry eye)	2 months (instilled 3 times daily)	• Sodium hyaluronate improvement of comfort & reduction in CD44 expression superior when compared with CMC • CMC caused blurred vision
Dausch et al. [10]	• Tears Again liposomal spray • Eye gel containing triglycerides	• LIPCOF • TBUT • Schirmer's • Eyelid health • Visual acuity • Subjective reports	Randomised controlled, multi-centre, crossover study	74 (100% lipid layer disturbances[14])	6 weeks (instilled 3 times daily)	• LIPCOF, TBUT, Schirmer's, eyelid health, visual acuity & comfort were superior after liposomal spray treatment
Johnson et al. [2]	• Sodium hyaluronate (0.1%) • Sodium hyaluronate (0.3%) • Saline (control)	• NITBUT • Subjective reports	Randomised controlled crossover study	13 (100% moderate dry eye)	6 h	• NITBUT & comfort improvement was greater with sodium hyaluronate 0.3% than 0.1%
Craig et al. [9]	• Tears Again Liposomal spray • Saline (control)	• LLG • NITBUT • TMH • Subjective reports	Randomised, double-masked, contralateral eye study	22 (18% had borderline dry eye according to McMonnies Dry Eye Questionnaire[13])	135 min (single application)	• LLG, NITBUT & comfort improvement was superior after liposomal spray treatment • TMH did not change
Lee et al. [3]	• Sodium hyaluronate (0.1%) • CMC (0.5%)	• NaFl staining • TBUT • Subjective reports	Randomised, double-masked, non-crossover study	65 (100% mild to moderate dry eye according to unspecified criteria)	8 weeks (6 times daily)	• NaFl staining, TBUT & symptoms improvement was not significantly different between treatment types
Evangelista et al. [17]	• Carnidrop • Optive • Blu Sal	• TBUT • Ocular protection index	Randomised, double-masked, non-crossover study	27 (moderate − DEWS classification)	15 and 60 min	• Carnidrop outperformed comparators
Pult et al. [11]	• Optrex ActiMist • Dry Eyes Mist • Tear Mist	• OSDI • NITBUT	Randomised, multi-centred, double-masked, contralateral eye study	80 (26.9% had dry eye according to OSDI)	10 min (single application)	• Optrex ActiMist significantly improved OSDI & NITBUT • Tear Mist & Dry Eyes Mist reduced OSDI & NITBUT
Baeyens et al. [18]	• Hyaluronate sodium (0.18%) • Carbomer (0.3%) • Saline	• Symptoms • Fluorescein staining	Randomised, double-masked, non-crossover study	304	84 days (instilled 2–4 times daily)	• Sodium hyluronate outperformed other treatments
Barabino et al. [19]	• Hyaluronic acid and tamarind seed polysaccharide • Carmellose sodium	• OSDI • TBUT • Schirmer • Corneal & conjunctival staining	Randomised, double-masked, non-crossover study	49 (moderate dry eye)	3 months (instilled 4 times daily)	• Formulations equally effective in reducing symptoms and staining. No effect on tear volume.
Simmons et al. [20]	• Lipid-based tear formulations containing carboxymethylcellulose, glycerin, polysorbate 80, and emulsified lipid	• Subjective Evaluation of Symptom of Dryness • OSDI	Randomised, double-masked, non-crossover study	256 (reduced TBUT and staining)	3 months (instilled 1–2 times daily)	• Formulations non-inferior to existing lipid based product
Simmons et al. [21]	• Carmellose sodium • Hyaluronic acid at different concentrations and osmoprotectants • Standard carmellose sodium-containing formulation (Refresh Tears)	• OSDI	Randomised, double-masked, non-crossover study	305 (mild-to-moderate signs of dry eye, an OSDI score of 18–65, TBUT < 10 s & currently using artificial tears	3 months (instilled ≥ 2 times daily)	• Reduction in symptoms with all formulations, but differences between them in patients with pre-existing staining.
Perez-Balbuena et al. [22]	• Xanthan gum • Chondroitin sulfate preservative free	• Schirmer • TBUT • OSDI	Randomised, double-masked, non-crossover study	148	2, 7, 15, 30 and 60 days	• Xanthan gum/chondroitin sulfate preservative free showed similar clinical efficacy