*Original Research Article*

Expert perspectives on the management of moderate to severe dry eye disease in Indian Settings

ABSTRACT

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| **Objective**: To assess ophthalmologists’ clinical perspectives on the burden, diagnosis, and management of moderate to severe dry eye disease (DED), with a particular focus on the use of trehalose-based formulations in Indian settings.  **Methods**: The cross-sectional study was conducted across India using a 23-item questionnaire to evaluate clinicians' perspectives on DED, including its prevalence, demographics, diagnostic approaches, treatment preferences, management challenges, and use of therapies such as trehalose. Data were analyzed using descriptive statistics, with categorical variables presented as percentages.  **Results**: The study included responses from 192 ophthalmology experts. Nearly half of the clinicians (46.88%) preferred trehalose as a lubricant for managing moderate to severe DED, particularly after cataract surgery. The majority (42.71%) had been using trehalose eye drops for 3–5 years, and approximately 68% reported switching to trehalose when patients showed an inadequate response to carboxymethylcellulose 0.5%. About 45% of the experts noted that the most common dosing regimen was four times daily. Improvement in Schirmer’s values and tear breakup time (TBUT) by week eight was observed by around 46% of clinicians. A large majority of respondents (80.73%) stated that trehalose acts through multiple mechanisms, including induction of autophagy, protection against oxidative stress, and preservation of labile proteins. Most clinicians (89.06%) acknowledged its benefits in preserving corneal structure, enhancing the ocular surface, and relieving DED symptoms. Half of the respondents typically prescribed trehalose for 12 weeks.  **Conclusion**: The study highlights the growing preference for trehalose-based eye drops in managing moderate to severe DED, especially post-cataract surgery, among Indian clinicians. Consistent clinical improvements and recognition of trehalose’s multifaceted mechanisms support its use, particularly when conventional lubricants are ineffective. |

***Keywords****: Dry eye disease, Cataract surgery, Artificial tears, Tear substitutes, Trehalose*

1. INTRODUCTION

Dry eye disease (DED) is one of the most common ocular conditions and a leading cause of ophthalmology visits worldwide, affecting millions worldwide, with a prevalence ranging from 5% to 50% depending on geographic region [1,2]. Its chronic nature leads to reduced productivity and workplace performance, contributing to a substantial economic burden on both individuals and healthcare systems [3-10].

The prevalence of DED in India varies widely across regions. A recent hospital-based study from North India reported a prevalence of 32%, with most cases classified as moderate to severe [11]. An Indian observational hospital-based study of 1,458,830 individuals reported a DED incidence of 2,688 per million in children and 16,482 per million in adults. With India’s rapidly aging population, increasing urban migration, and the rise of a digitally engaged middle class, the burden of DED is expected to escalate further, signaling a potential public health concern that warrants early recognition and structured intervention [12].

Managing the burden of DED requires a comprehensive approach, with artificial tear drops serving as the first-line treatment due to their ease of use, wide availability in various formulations, and favorable safety profile. The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II management and therapy subcommittee recommends tear substitutes as the initial step in DED management [13]. Trehalose, a tear substitute and natural disaccharide composed of two glucose molecules, is emerging as a promising therapeutic option for DED. Known for its cell-protective, antioxidant, and anti-inflammatory properties, trehalose stabilizes proteins and cell membranes, prevents denaturation, and inhibits oxidative damage. These features make it particularly suitable for addressing the multifactorial pathophysiology of DED [14].

This study aims to explore the clinical perspectives of ophthalmologists in India regarding the prevalence, diagnostic strategies, and therapeutic approaches to moderate to severe DED, with an emphasis on the adoption and perceived benefits of trehalose-based lubricants.

2. materialS and methods

A cross-sectional study was conducted among ophthalmologists in managing DED in Indian settings from June 2024 to December 2024. The study was performed after obtaining approval from Bangalore Ethics, an Independent Ethics Committee, which was recognized by the Indian Regulatory Authority, the Drug Controller General of India.

An invitation was sent to clinical professionals across India based on their expertise and experience in treating DED in the month of March 2024 for participation in this Indian survey. About 192 clinicians from major cities of all Indian states, representing the geographical distribution, shared their willingness to participate and provide necessary data. Clinicians had the discretion to skip questions they did not wish to answer. Written informed consent was obtained from all participants, who were required to independently complete the questionnaire without consulting peers. Unanswered questions were treated as non-attempts.

The questionnaire booklet titled TREND (Trehalose Usage in Dry Eye Management: Expert Perspective Study) was sent to the doctors who were interested in participating in this study. The TREND study questionnaire comprised a 23-item multiple-response questionnaire that explored the key aspects of DED, including its estimated prevalence, demographic patterns, diagnostic approaches, treatment preferences, management challenges, and clinician experience with specific therapies such as carboxymethylcellulose and trehalose.

**Statistical analysis**

The data were analyzed using descriptive statistics, with categorical variables expressed as percentages to illustrate their distribution. Each variable’s frequency and corresponding percentage were reported to provide a comprehensive overview. To visually represent the distribution of categorical variables, pie and bar charts were generated using Microsoft Excel 2013 (version 2409, build 16.0.18025.20030).

3. results

The study included 192 participants. More than half of the experts (53.65%) reported that 11–25% of the patients presenting to routine practice have moderate to severe dry eye. Nearly 49% stated that computer vision syndrome is the most commonly observed association with moderate to severe dry eye. According to 49% of respondents, middle-aged individuals are more commonly affected by moderate to severe dry eye in their practice. A significant proportion of clinicians (58.33%) considered periodic screening the most effective method for early diagnosis of moderate to severe DED. Over half (53.65%) indicated that 26–50% of their patients with moderate to severe DED are diagnosed with aqueous-deficient dry eye, while 46% reported that 26–50% of patients with severe DED are diagnosed with evaporative dry eye.

Approximately 40% of clinicians preferred using a combination of patient history, Schirmer score, and slit-lamp examination to diagnose DED in their routine practice. According to 38% of experts, there is uncertainty about whether an urban–rural divide exists in the incidence of moderate to severe DED. The majority of clinicians (77.60%) emphasized a comprehensive approach, comprising regular medication use, screen time management, visual hygiene, and lifestyle modifications, as most effective for achieving favorable clinical outcomes in DED. As per 39% of participants, 15–30% of their patients who undergo cataract surgery develop moderate to severe DED.

Nearly half of the clinicians (51.04%) favored a comprehensive intraoperative strategy, incorporating ocular surface coating with viscoelastic, avoiding excessive use of irrigating fluids, anesthetic agents, and povidone-iodine, and preventing phototoxicity through the use of microscope filters, to help minimize the risk of worsening DED during cataract surgery in patients with pre-existing DED. Most experts (83.33%) reported regularly prescribing lubricants after cataract surgery. Around 41% indicated that 11–25% or 26–50% of their patients with moderate to severe dry eye do not respond to 0.5% carboxymethylcellulose eye drops. According to 47% of clinicians, 11–20% of their patients with moderate to severe DED present with chronic inflammation.

Nearly half of the clinicians (46.88%) identified trehalose as their preferred lubricant for managing patients with moderate to severe DED following cataract surgery (Table 1). Approximately 43% reported using trehalose eye drops for 3–5 years (Fig. 1). A significant proportion of clinicians (68.75%) indicated that they switched to trehalose in patients unresponsive to 0.5% carboxymethylcellulose (Table 2).

**Table 1: Distribution of responses to clinicians’ most preferred lubricant for patients with moderate to severe DED following cataract surgery**

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| **Lubricant type** | **Response rate (n = 192)** |
| Trehalose | 90 (46.88%) |
| Carboxymethylcellulose eye drops 0.5% | 10 (5.21%) |
| Polyethylene glycol + propylene glycol combination eye drops | 27 (14.06%) |
| Sodium hyaluronate eye drops | 63 (32.81%) |
| Hydroxypropyl methylcellulose gel 0.3% | 2 (1.04%) |

**Fig. 1: Distribution of responses to duration of trehalose eye drop usage in clinical practice for management of DED**

**Table 2: Distribution of responses to clinicians’ preferred strategy for patients unresponsive to carboxymethylcellulose 0.5% eye drops**

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| **Preferred strategy** | **Response rate (n = 192)** |
| Change from carboxymethylcellulose to trehalose | 132 (68.75%) |
| Change from carboxymethylcellulose 0.5% to carboxymethylcellulose 1.0% | 44 (22.92%) |
| Increase the frequency of the dose for carboxymethylcellulose 0.5% | 16 (8.33%) |

As recommended by the majority (45.31%) of clinicians, the most frequently endorsed dosage regimen for trehalose in patients with moderate to severe DED is four times daily (Fig. 2). Approximately 46% observed an improvement in Schirmer’s values and tear breakup time (TBUT) by the eighth week of trehalose use (Table 3).

**Fig. 2: Distribution of responses to recommended dosage of trehalose for patients with moderate to severe DED**

**Table 3: Distribution of responses to time taken for trehalose-induced improvement in Schirmer's values and TBUT in moderate to severe DED**

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| **Improvement in the Schirmer's values and TBUT** | **Response rate (n = 192)** |
| After 6 weeks | 81 (42.19%) |
| After 8 weeks | 88 (45.83%) |
| After 12 weeks | 23 (11.98%) |

A substantial majority of clinicians (80.73%) believed that trehalose exhibits a comprehensive mechanism of action, including the induction of cellular autophagy, protection against oxidative stress, mitigation of pathological protein aggregation, and preservation of labile proteins (Fig. 3). Most experts (89.06%) recognized that trehalose offers multiple advantages, such as preserving corneal structure, enhancing the ocular surface, and relieving signs and symptoms of DED (Table 4). Half of the respondents (50%) indicated that they typically prescribe trehalose for 12 weeks in patients with DED (Fig. 4).

**Fig. 3: Distribution of responses to clinicians’ perspectives on the novel mechanism of action of trehalose**

**Table 4: Distribution of responses to clinicians’ opinions on the advantages of trehalose in ocular therapy**

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| **Reported advantage** | **Response rate (n = 192)** |
| Preserves morphological and morphometric features of the corneal epithelium | 4 (2.08%) |
| Significant improvements on the ocular surface | 8 (4.17%) |
| Reduction in the signs and symptoms of DED | 9 (4.69%) |
| All of the above | 171 (89.06%) |

**Fig. 4: Distribution of responses to the duration of trehalose prescription for patients with DED in clinical practice**

4. discussion

The study findings highlight key trends in the diagnosis and management of moderate to severe DED in Indian clinical settings. Notably, the significant preference for trehalose among surveyed clinicians underscores its emerging role as a leading therapeutic option in this patient population.

The majority of the clinicians preferred trehalose for managing patients with moderate to severe DED following cataract surgery. This aligns with growing clinical evidence supporting the efficacy of trehalose-based formulations. A prospective study by Mencucci et al. demonstrated that the perioperative use of a hyaluronic acid and trehalose ophthalmic solution significantly reduced signs and symptoms of DED following cataract surgery in patients with mild to moderate DED. Patients who received the solution both before and after surgery showed the greatest benefit, with significantly lower Ocular Surface Disease Index (OSDI) scores and more stable tear film break-up time compared to those who received treatment only after surgery or received no treatment [15]. Similarly, a randomized controlled trial by Cagini et al. demonstrated that trehalose 3% combined with hyaluronic acid 0.15% eye drops effectively reduced ocular surface inflammation and dry eye symptoms following cataract surgery in patients with a healthy ocular surface. The findings showed that the combination treatment led to earlier and more pronounced improvements in tear film stability, dry eye symptoms, and ocular surface integrity, as evidenced by TBUT, Schirmer test, and corneal fluorescein staining [16].

The finding that most clinicians (42.71%) have been using trehalose for 3–5 years indicates its increasing integration into clinical practice, despite being relatively newer than traditional lubricants. This adoption pattern suggests growing confidence in trehalose's efficacy based on clinical experience. Furthermore, the high percentage of clinicians (68.75%) who switched to trehalose after unsatisfactory results with carboxymethylcellulose 0.5% highlights potential limitations of conventional treatments and the need for alternatives with different mechanisms of action. A randomized controlled trial by Matsuo et al. found that trehalose solution was more effective in treating moderate to severe dry eye syndrome compared to two commercially available eye drops containing either hyaluronan or hydroxyethyl cellulose [17].

The observed improvements in objective clinical parameters, specifically Schirmer's test values and TBUT by the eighth week of treatment (reported by 45.83% of clinicians), provide preliminary support for trehalose's clinical efficacy. In a study by Pinto-Bonilla involving patients with moderate-to-severe dry eye syndrome, treatment with a combination of trehalose and hyaluronic acid showed a trend toward improvement in both Schirmer test scores and TBUT, indicating potential benefits for tear production and stability [18]. An Indian study by Morya et al. found that treatment with a sodium hyaluronate–trehalose combination resulted in greater improvements in Schirmer’s test values and TBUT after eight weeks of consistent use in patients with DED, with the benefits being especially pronounced in those with severe DED [19].

Schmidl et al. investigated the effects of a single dose of various eye drops on tear film thickness (TFT) in patients with mild to moderate DED, using high-resolution optical coherence tomography. The combination of trehalose (30 mg/mL) and sodium hyaluronate (1.5 mg/mL) led to a significant increase in TFT, from 2.4 ± 0.4 μm to 3.1 ± 0.9 μm, within 10 minutes of installation, with the effect lasting up to 240 minutes. In contrast, sodium hyaluronate alone (HA) produced a shorter-lasting increase in TFT, while saline (NaCl) showed no significant change. These findings suggest that trehalose-containing eye drops offer a more sustained improvement in tear film stability and may be particularly beneficial for managing dry eye symptoms [20].

A significant proportion of clinicians (80.73%) in the current study recognized the multifaceted mechanism of action of trehalose. This awareness of its cellular protective properties, including induction of autophagy, protection against oxidative stress, prevention of protein aggregation, and preservation of proteins, indicates that clinicians value its biological plausibility beyond simple lubrication. This understanding may contribute to the broad clinical support for trehalose, with 89.06% of clinicians acknowledging its comprehensive benefits for corneal structure, ocular surface enhancement, and symptom relief. The preferential dosing regimen of four times daily (45.31%) and typical treatment duration of 12 weeks (50%) provides practical insights into clinical guidance to obtain optimal therapeutic results.

Hill-Bator et al. evaluated the cytoprotective effects of trehalose-based eye drops compared to seven commercially available treatments during experimental desiccation of cultured human corneal epithelial cells. The trehalose formulation demonstrated superior protection, significantly reducing cell death, preserving membrane integrity, maintaining normal cell morphology, and supporting proliferative activity. Among all tested preparations, trehalose-based drops were the most effective in safeguarding cells from desiccation-induced damage, highlighting their potential advantage in dry eye treatment [21]. In a study by Panigrahi et al., trehalose was found to reduce stress-induced inflammation in corneal cells by inhibiting p38 mitogen-activated protein kinase (MAPK) activation and promoting autophagy. Trehalose-treated cells showed increased expression of autophagy markers LC3II and lysosomal-associated membrane protein 1 (LAMP1) compared to untreated controls. Additionally, trehalose significantly decreased both mRNA and protein levels of pro-inflammatory cytokines Interleukin (IL)-6, IL-8, and MCP-1 under tumor necrosis factor-α (TNF-α)and desiccation-induced stress. The study also demonstrated that trehalose reduced stress-induced phosphorylation of p38 MAPK, highlighting its potential anti-inflammatory and cytoprotective role in ocular surface health [22]. In a desiccation-induced dry eye model in mice, trehalose application effectively restored ocular surface integrity, reduced keratinization, and suppressed the expression of inflammatory and proteolytic markers, including MMP-9 and HSP70 [23].

A comprehensive systematic review of randomized controlled trials by Ballesteros-Sánchez concluded that trehalose-based tear substitutes consistently outperformed control treatments across all measured outcomes in patients with DED. Improvements included a reduction in OSDI scores by −8.5 ± 7 points, an increase in TBUT by 1.9 ± 1 seconds, TFT by 0.25 ± 0.1 μm, tear meniscus height (TMH) by 0.02 ± 0.02 mm, and Schirmer test results by 0.8 ± 1.4 mm. Additionally, corneal fluorescein staining improved by −0.7 ± 0.1 points, and visual acuity increased by 0.3 ± 2.1 letters. Importantly, no adverse events were reported [24]. These findings support the use of trehalose tear substitutes as a safe and effective option for managing DED and recommend their consideration in routine clinical practice.

The present study holds significant relevance as it captures expert opinion focused on evidence-based clinical practices, using a carefully designed and validated questionnaire. These findings can support more informed decision-making regarding optimal treatment strategies, ultimately aiming to enhance patient outcomes in DED care. However, certain limitations should be acknowledged. The relatively small sample size may affect the generalizability of the results, as a larger and more diverse cohort could offer a more representative view of the broader DED patient population. Furthermore, reliance on expert opinion introduces a potential risk of bias, as individual experiences and preferences may have influenced the conclusions drawn. Therefore, while the findings are valuable, they should be interpreted with these limitations in mind, and further research is recommended to validate and expand upon the current results.

4. Conclusion

This study validates the growing clinical preference for trehalose-based eye drops in the management of moderate to severe DED, particularly in patients following cataract surgery. The findings indicate consistent improvements in clinical outcomes such as Schirmer’s test values, TBUT, and symptom relief, along with recognition of trehalose’s multifaceted mechanism of action. Its widespread use, especially when conventional lubricants fall short, reflects its perceived therapeutic advantage.

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