Journal of Health and Rehabilitation Research 2791-156X JHRR

Original Article

Effect of N-Acetyl Cysteine in the Treatment of Dry Eye Disease

Dr. Huzaifa Malik[1], Dr. Shagufta Parveen[1], Dr. Ijlal Taimoor[1], Dr. Umar Ijaz[1], Dr. Jaweria Zahid[1], Dr. Shahzad Raza, Dr. Muhammad Farukh Habib[*2]

[1] Resident Ophthalmology, Armed Forces Institute of Ophthalmology, Pak-Emirates Military Hospital, Rawalpindi., Pakistan

[2] Department of Management Sciences, Shifa Tameer E Millat University Islamabad, Pakistan.

Corresponding author: muhammadfarrukhhabib@gmail.com

Keywords: Dry Eye Disease, N-Acetyl Cysteine, Tear Film Break-Up Time, Schirmer's Test, Ocular Surface Inflammation, Therapeutic Agents, Tear Film Stability.

Abstract

Background: Dry eye disease (DED) is a multifactorial disorder characterized by tear film instability, ocular surface inflammation, and symptoms of discomfort that significantly impact patients' quality of life. Current treatments often provide only temporary relief, necessitating the exploration of novel therapeutic agents such as N-acetyl cysteine (NAC) to target underlying pathophysiological mechanisms.

Objective: To evaluate the efficacy of N-acetyl cysteine in improving tear film stability and alleviating symptoms in patients with dry eye disease.

Methods: This quasi-experimental study was conducted at the Department of Ophthalmology, Pak-Emirates Military Hospital, Rawalpindi, from January 2022 to May 2024. Sixty-six patients (132 eyes) aged 18-65 years, diagnosed with bilateral DED for at least three months, were enrolled. Participants were alternately assigned to the intervention group, which received NAC eye drops (0.1% w/v) administered as one drop every six hours, or the control group, which received sterile saline artificial tears (0.9%) at the same frequency. Baseline demographic and clinical data were collected. Tear Film Break-Up Time (TBUT) and Schirmer's test scores were measured at baseline, two weeks, one month, and three months post-treatment. Additionally, symptoms of burning, itching, and foreign body sensation were assessed using a four-point scale. Data were analyzed using SPSS version 25.0, with a p-value of ≤0.05 considered statistically significant.

Results: The median age of participants was 34.50 years (IQR: 16.00), with 35 (53.0%) being male. Significant improvements were observed in the NAC group compared to the control group at one and three months post-treatment. TBUT increased from a median of 7.00 seconds (IQR: 5.00) at baseline to 15.50 seconds (IQR: 8.00) at three months ($p<0.001$). Schirmer's test scores improved from a median of 5.00 mm (IQR: 2.00) at baseline to 11.00 mm (IQR: 5.00) at three months ($p<0.001$). The NAC group also experienced a significant reduction in foreign body sensation at three months ($p=0.023$).

Conclusion: N-acetyl cysteine is an effective treatment for improving tear film stability and reducing symptoms associated with dry eye disease. Its use offers significant benefits in both objective clinical measures and patient-reported outcomes, making it a valuable therapeutic option for managing DED.

1 Introduction

Dry eye disease (DED) is a prevalent and complex condition characterized by a disturbance in the homeostasis of the tear film, leading to symptoms of ocular discomfort, visual disturbance, and potential damage to the ocular surface. It is a multifactorial disorder where the underlying causes often include tear film instability, increased tear osmolarity, and inflammation of the ocular surface, all of which contribute to the pathogenesis and progression of the disease. Despite its widespread occurrence and significant impact on the quality of life, DED remains challenging to manage due to its intricate etiology and chronic nature (1). Current treatment strategies for DED primarily focus on symptom relief, utilizing artificial tears, anti-inflammatory agents, and lifestyle modifications. However, these approaches often provide only temporary relief, necessitating the exploration of novel therapeutic agents that can target the underlying pathophysiological mechanisms of DED, offering more effective and sustained treatment outcomes (2, 3).

One such promising therapeutic agent is N-acetyl cysteine (NAC), a derivative of the amino acid cysteine and a precursor to the antioxidant glutathione. NAC is well known for its mucolytic properties, particularly in respiratory diseases, where it works by breaking down mucin disulfide bonds, thereby reducing the viscosity of mucus. This same mechanism is believed to play a crucial role in improving tear film stability in patients with DED by reducing tear film viscosity and enhancing tear film break-up time (4, 5). Additionally, NAC's potent

antioxidant properties may help mitigate oxidative stress—a key factor implicated in the exacerbation of DED—by scavenging reactive oxygen species (ROS) and reducing the inflammatory response on the ocular surface (6, 7). The tear film in DED patients is often characterized by elevated levels of ROS and pro-inflammatory cytokines, contributing to cellular damage and further inflammation. By bolstering the antioxidant defenses of the ocular surface, NAC could potentially alleviate these pathological processes, offering both symptomatic relief and a reduction in the progression of the disease (8).

While the application of NAC in ophthalmology is not entirely new, with its use documented in conditions such as filamentary keratitis and certain corneal diseases, its specific efficacy in the management of DED warrants further exploration. Previous studies have suggested that NAC may be beneficial in this context, but the evidence remains limited and inconclusive, highlighting the need for more rigorous clinical trials to establish its role in DED management. This study aims to address this gap by evaluating the effectiveness of NAC in improving tear film stability and alleviating the symptoms of DED. By focusing on objective measures such as tear film break-up time and Schirmer's test, alongside subjective symptom assessment, this research seeks to provide a comprehensive evaluation of NAC's therapeutic potential in DED. The findings from this study could contribute to the development of more effective treatment protocols, ultimately improving the quality of life for patients suffering from this debilitating condition (9, 10).

2 Material and Methods

This quasi-experimental study was conducted at the Department of Ophthalmology, Pak-Emirates Military Hospital, Rawalpindi, between January 2022 and May 2024. The study aimed to evaluate the efficacy of N-acetyl cysteine (NAC) in treating dry eye disease (DED) compared to sterile saline artificial tears. A total of 66 patients, corresponding to 132 eyes, aged between 18 and 65 years and diagnosed with bilateral DED for at least three months, were included. Participants were selected using consecutive, non-probability sampling and assigned to the intervention or control groups in an alternating manner(11,12).

Patients with contact lenses, a history of ocular surgery within the past six months, active ocular infections or inflammation, use of systemic medications affecting tear production, or known hypersensitivity to NAC were excluded. Before enrollment, all patients provided informed consent, and in the case of minors, consent was obtained from a parent or guardian. The study protocol was designed following the ethical principles outlined in the Declaration of Helsinki and adhered to the institutional guidelines of the Pak-Emirates Military Hospital. Ethical approval for the study was obtained from the hospital's ethical review committee.

At baseline, comprehensive demographic and clinical data were collected, including patient age, gender, and duration of symptoms. The intervention group received NAC eye drops (0.1% w/v), administered as one drop every six hours, while the control group was given sterile saline artificial tears (0.9%) at the same frequency. Both groups were re-assessed at two weeks, one month, and three months after initiating treatment(13,14).

The primary outcomes measured were Tear Film Break-Up Time (TBUT) and Schirmer's test scores. TBUT was evaluated by instilling fluorescein dye into the conjunctival sac and recording the time until the first dry spot appeared on the cornea. Schirmer's test was performed by placing a strip of filter paper in the lower eyelid and measuring the length of wetting (in millimeters) after five minutes. Additionally, patients were asked to subjectively rate their symptoms of eye burning, itching, and foreign body sensation at baseline and three months post-treatment using a four-point scale, where 0 indicated the absence of symptoms, and 3 indicated severe symptoms.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data, with means and standard deviations or medians and interquartile ranges calculated for continuous variables, and frequencies and percentages for categorical variables. The Shapiro-Wilk test was applied to assess the normality of the data. For comparisons between the intervention and control groups, the independent samples t-test or Mann-Whitney U test was used for continuous variables, depending on the distribution, and the Chi-square test or Fisher's exact test was used for categorical variables. A p-value of ≤0.05 was considered statistically significant.

This methodological approach ensured a thorough and scientifically rigorous evaluation of NAC's potential in managing dry eye disease, providing reliable data for further clinical consideration and research.

3 Results

The study included 66 patients, accounting for 132 eyes, with a median age of 34.50 years (IQR: 16.00). Of these, 35 (53.0%) were male. The median duration of dry eye symptoms before enrollment was 14.00 months (IQR: 9.00). Baseline characteristics, including age, gender distribution, and symptom duration, were comparable between the intervention and control groups, with no statistically significant differences observed (p>0.05) (Table 1).

Table 1: Patient Characteristics According to Treatment Group

Variable	NAC Group (n=66)	Control Group (n=66)	p-value
Age (years)	30.0 (IQR: 16.0)	38.0 (IQR: 18.0)	0.104
Gender			0.459
- Males	16 (48.5%)	19 (57.6%)	
- Females	17 (51.5%)	14 (42.4%)	
Complaint Duration (months)	13.00 (IQR: 10.00)	15.00 (IQR: 6.00)	0.132

Tear Film Break-Up Time (TBUT) and Schirmer's test scores were measured at baseline, two weeks, one month, and three months after initiating treatment. Both groups had similar baseline TBUT and Schirmer's test scores. However, significant improvements were observed in the NAC group at one month and three months post-treatment compared to the control group (Table 2).

Table 2: Tear Film Break-Up Time and Schirmer's Test Scores According to Treatment Group

Variable	NAC Group (n=66)	Control Group (n=66)	p-value
TBUT (seconds)			
- Baseline	7.00 (IQR: 5.00)	6.00 (IQR: 5.00)	0.251
- Two weeks	7.00 (IQR: 5.00)	6.00 (IQR: 5.00)	0.305
- One month	11.00 (IQR: 6.00)	8.00 (IQR: 7.00)	0.001
- Three months	15.50 (IQR: 8.00)	11.50 (IQR: 10.00)	<0.001
Schirmer's Test (mm)			
- Baseline	5.00 (IQR: 2.00)	5.00 (IQR: 2.00)	0.629
- Two weeks	6.00 (IQR: 2.00)	6.00 (IQR: 2.00)	0.103
- One month	9.00 (IQR: 4.00)	7.00 (IQR: 4.00)	0.038
- Three months	11.00 (IQR: 5.00)	8.50 (IQR: 3.00)	<0.001

At the two-week assessment, there were no significant differences between the groups in TBUT or Schirmer's test scores, indicating similar initial responses to treatment (p=0.305 and p=0.103, respectively). However, by one month, the NAC group exhibited a statistically significant improvement in TBUT (p=0.001) and Schirmer's test scores (p=0.038) compared to the control group. These differences became even more pronounced at three months, with the NAC group showing superior outcomes for both TBUT (p<0.001) and Schirmer's test scores (p<0.001).

In terms of symptom relief, the NAC group demonstrated a significant reduction in foreign body sensation at the three-month mark compared to the control group (p=0.023), as shown in Table 3. However, no significant differences were noted between the groups in burning or itching sensations at three months (p>0.05).

Table 3: Symptom Scores According to Treatment Group

Symptom	NAC Group (n=66)	Control Group (n=66)	p-value
Burning Sensation			
- Baseline	2.00 (IQR: 1.00)	2.00 (IQR: 1.00)	0.926
- Three months	1.00 (IQR: 1.00)	1.00 (IQR: 1.00)	0.758
Itching Sensation			
- Baseline	1.00 (IQR: 2.00)	1.00 (IQR: 1.00)	0.569
- Three months	1.00 (IQR: 1.00)	1.00 (IQR: 1.00)	0.326
Foreign Body Sensation			
- Baseline	2.00 (IQR: 1.00)	1.00 (IQR: 1.00)	0.147
- Three months	0.00 (IQR: 1.00)	1.00 (IQR: 1.00)	0.023

Overall, the results of this study demonstrate that N-acetyl cysteine is effective in improving tear film stability and reducing symptoms associated with dry eye disease over a three-month treatment period. No complications or adverse effects were reported in either treatment group during the study period.

4 Discussion

The present study investigated the efficacy of N-acetyl cysteine (NAC) in the management of dry eye disease (DED) and demonstrated that NAC significantly improves tear film stability and alleviates certain symptoms associated with DED, particularly foreign body sensation, over a three-month period. These findings are consistent with previous research that has highlighted the potential of NAC as a therapeutic

agent in various ocular conditions, including DED. The results of this study add to the growing body of evidence supporting the use of NAC in enhancing tear film break-up time (TBUT) and Schirmer's test scores, which are critical indicators of tear film stability and tear production, respectively (11, 15,16).

In comparison with earlier studies, the improvements observed in TBUT and Schirmer's test scores in the NAC group were significant, particularly at the one- and three-month follow-ups. This aligns with previous findings by Nepp et al. and Akyol-Salman et al., who reported that NAC effectively increased TBUT and Schirmer's test scores in patients with DED and other related conditions (11, 17, 18). The observed delay in the onset of significant improvement, with notable effects becoming evident after one month of treatment, suggests that NAC may require a period of sustained application to fully exert its therapeutic benefits. This temporal aspect of NAC's effectiveness could be related to its mechanism of action, which involves the gradual reduction of tear film viscosity and the enhancement of antioxidant defenses on the ocular surface (7, 14,19).

However, it is important to recognize the limitations of this study. The relatively small sample size of 66 patients (132 eyes) may limit the generalizability of the findings, and the follow-up period of three months, while adequate for observing initial treatment effects, does not provide insight into the long-term efficacy and safety of NAC. Larger studies with extended follow-up periods are necessary to confirm these results and establish the durability of NAC's therapeutic effects in DED management. Furthermore, although the study attempted to match baseline characteristics between the intervention and control groups, potential unmeasured confounding factors may have influenced the outcomes. The subjective nature of symptom reporting, despite the use of standardized questionnaires, introduces a degree of bias that is inherent in studies of this nature. These factors should be considered when interpreting the results and planning future research (13, 20).

The study's strengths lie in its rigorous methodology, including the use of well-established clinical measures such as TBUT and Schirmer's test, as well as the standardized assessment of symptoms. The consecutive, non-probability sampling and the alternating assignment of patients to treatment groups minimized selection bias, enhancing the internal validity of the findings. Additionally, the study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki, ensuring that patient safety and ethical considerations were prioritized throughout the research process (12,21).

In light of these findings, NAC appears to be a promising adjunctive therapy for patients with DED, particularly for those who do not respond adequately to conventional treatments such as artificial tears. The significant reduction in foreign body sensation observed in this study suggests that NAC may be particularly beneficial in alleviating the discomfort that is often most distressing for patients with DED. However, given the limitations discussed, it is recommended that future studies explore the long-term effects of NAC, investigate its efficacy in larger and more diverse patient populations, and assess its potential in combination with other therapeutic modalities.

In conclusion, this study contributes valuable evidence supporting the use of N-acetyl cysteine in the management of dry eye disease. While the results are promising, further research is needed to fully understand the role of NAC in DED treatment and to optimize its use in clinical practice. The findings of this study suggest that NAC not only improves objective measures of tear film stability but also provides significant symptomatic relief, highlighting its potential as a beneficial treatment option for patients suffering from this challenging and often debilitating condition.

5 Conclusion

In conclusion, the findings of this study underscore the potential of N-acetyl cysteine (NAC) as an effective therapeutic agent in the management of dry eye disease (DED). NAC demonstrated significant improvements in both objective clinical measures, such as Tear Film Break-Up Time (TBUT) and Schirmer's test scores, as well as in alleviating subjective symptoms, particularly foreign body sensation, over a three-month treatment period. These results suggest that NAC not only enhances tear film stability but also provides meaningful symptomatic relief, positioning it as a valuable addition to the current treatment modalities for DED. Despite the limitations of the study, including a relatively small sample size and a short follow-up period, the consistent and statistically significant improvements observed in the NAC group highlight its promise as a viable treatment option for DED patients who may not fully benefit from conventional therapies. Future research with larger, more diverse patient populations and longer follow-up periods is warranted to further establish the long-term efficacy and safety of NAC in managing DED. Ultimately, this study contributes to the growing body of evidence supporting NAC's role in addressing the complex pathophysiology of DED, offering hope for more effective and sustained management of this challenging condition.

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Disclaimers	
Author Contributions	All authors contributed to the conception and design of the study. Dr. Huzaifa Malik, Dr. Shagufta Parveen, Dr. Ijlal Taimoor, Dr. Umar Ijaz, Dr. Javeria Zahid, and Dr. Shahzad Raza were involved in data collection and clinical assessments. Muhammad Farrukh Habib performed the data analysis and drafted the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.
Conflict of Interest	The authors declare that there are no conflicts of interest.
Data Availability	Data and supplements available on request to the corresponding author.
Funding	NA
Ethical Approval	Institutional Review Board (IRB) of Pak-Emirates Military Hospital, Rawalpindi.
Trial Registration	NA
Acknowledgments	NA

~ JHRR, ISSN: 2791-156X ~