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ORIGINAL ARTICLE

Efficacy of rinse and treat protocol and its acceptability in patients with dry eye disease

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Abstract

This questionnaire-based pilot study aimed to ascertain the efficacy of the rinse and treat protocol and its acceptability in patients with dry eye disease (DED). Sixty-three patients of DED already on lubricating eye drops, who volunteered to be part of this exploratory multicentric pilot, were included in this study. The use of eye drops was successful in 53 (84%) patients. 41.27% of the patients did not face any challenge while using the eye drops whereas an equal proportion of the patients said that it was too much hassle. Other challenges faced were forgetfulness (96.35%), difficulty in handling the bottle of eye drops (4.76%), inability to find the bottles (3.17%), eye pain (1.59%), and sticky drops (1.59%). All except three respondents said that it would be significantly easier if both eye drops were in one bottle. While the initial results of the R-n-T protocol are equivocal, further studies with a larger sample size and grouping of patients as per the severity of DED as well as objective evaluation of the change in same will help in deciding the true value of sequential administration of lubricating eye drops.

Introduction

The prevalence of dry eye disease (DED), with and without symptoms, ranges from 5 to 50%. The prevalence of DED based on signs only is even more variable, reaching up to 75% in some populations. The impact of DED on vision, quality of life, and psychological and physical correlates of pain and well-being are considerable. The economic burden of DED is also notable, especially the costs due to reduced work productivity.[1] The symptomatology of DED is also extremely variable and lacks standardization, which is why management of the problem requires attention to both objective (clinical) and subjective (patient comfort) endpoints. DED is known to significantly impact the quality of life of those affected, and its prevalence is only increasing with the increasing use of screen devices. The COVID-19 pandemic has further brought the issue into focus,[2] with several experts calling DED the twin pandemic.

The rinse and treat (R-n-T) protocol works on the premise that the discomfort from DED has two main components: The lack of lubrication due to tear film deficiency and the accumulated mucus and debris that may be proinflammatory. The "lighter drop" used initially is to rinse the eye of the accumulated mucus and debris as part of step 1 of dry eye treatment. After the rinse, the "heavier drop" is used to address the lack of lubrication. In case, the patient feels that the high-viscosity eye drops are uncomfortable or sticky, and the patient may use the "lighter drop" to dilute the effect of the "heavier drop."

To the best of our knowledge, there is no previous study that has addressed this treatment protocol which has proven to be clinically useful in our experience and that of several colleagues taking care of DED patients.

Methods

This questionnaire-based pilot study aimed to ascertain the efficacy of the R-n-T protocol and its acceptability in DED patients. Sixty-three patients of DED already on lubricating eye drops, who volunteered to be part of this exploratory multicentric study, were included in this study. All the study subjects were above 18 years of age, and those who were unable to administer their eye drops themselves were excluded from the study. Given the explorative nature of the study, no formal sample size has been calculated. Since there was no new medication, treatment regimen, or device being investigated, and the study subjects were all volunteers already on treatment for DED, no ethics committee approval was sought. The study complies with the ethical principles enshrined in the 1964 Declaration of Helsinki[3] and the WHO Guidelines for Good Clinical Practice for Trials.[4]

In the right eye, the study volunteers were asked to first administer the "lighter" drop. After a few calm blinks (2–5), they were asked to use the "heavier" drop. The volunteers were asked to continue with the eye drops as before in the left eye, which served as control. The frequency of the eye drops in both eyes was to be equal and as decided by the treating ophthalmologist during the clinical evaluation. The volunteers were also instructed to continue their usual lid hygiene and supportive therapy as before.

A validated questionnaire was administered by the principal investigator to ascertain the efficacy of the R-n-T protocol after 3 weeks of R-n-T protocol of eye drops use. The questionnaire was designed and validated to ascertain information about patient demographics, diagnosis, severity of DED, possible etiology and contributing factors, lifestyle changes during the study duration, and concomitant medications, if any.

Results

The mean age of the patients was 51.92 (SD = 17.06) years. There were 24 males and 39 females with a female-to-male ratio of 1.6. The majority of the participants used hyaluronate (54%) as the first lubricant followed by carboxymethylcellulose (CMC) 0.5% (22.2%), CMC 1% (11.1%), hydroxypropyl methylcellulose (HPMC) 0.3% (11.1%), and polyethylene glycol (1.6%). As a second lubricant, the majority of the participants were given CMC 0.5% (46%) followed by hyaluronate (22.2%), HPMC 0.3% (11.1%), CMC 1% (11.1%), and polyethylene glycol (4.8%) [Table 1 and Figure 1].

The majority of the patients were suffering from moderate (65.08%) type of clinical dry eye symptoms, whereas 19.05% of the patients suffered from mild type of eye symptoms, and 12.7% suffered from severe dry eye symptoms. 34.92% of the patients had a history of allergy, whereas 20.63% of the patients had a previous history of eye surgery and 9.52% of the patients had no etiology. The most common comorbidity among the patients was hypertension (42.86%) followed by diabetes mellitus (25.4%) and 31.75% of all the patients were taking medications [Table 2]. After the administration of drops, patients were asked about changes in daily activities during their follow-up visits and 87% of the patients reported no change in daily activities whereas 5% of the patients reported having flu [Figure 2].

Table 1: Details of lubricants

	n	%
Gender		
Female	39	61.90
Male	24	38.10
Total	63	100.00
First lubricant (salt)		
Hyaluronate	34	54
Carboxymethylcellulose 0.5%	14	22.2
Carboxymethylcellulose 1%	7	11.1
Hydroxypropyl methylcellulose 0.3%	7	11.1
Polyethylene glycol	1	1.6
Total	63	100
Second lubricant		
Carboxymethylcellulose 0.5%	29	46
Hyaluronate	14	22.2
Hydroxypropyl methylcellulose 0.3%	10	15.9
Carboxymethylcellulose 1%	7	11.1
Polyethylene glycol	3	4.8
Total	63	100

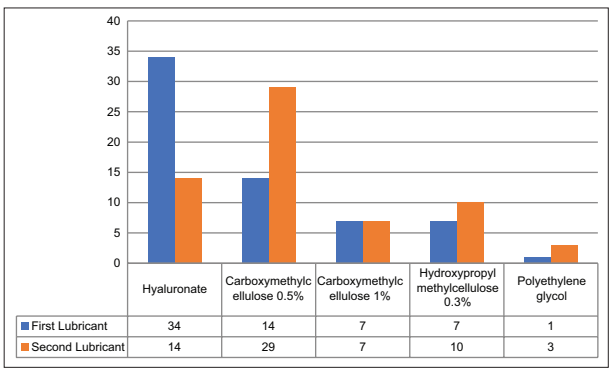

Figure 1: Comparison of the use of first and second lubricants

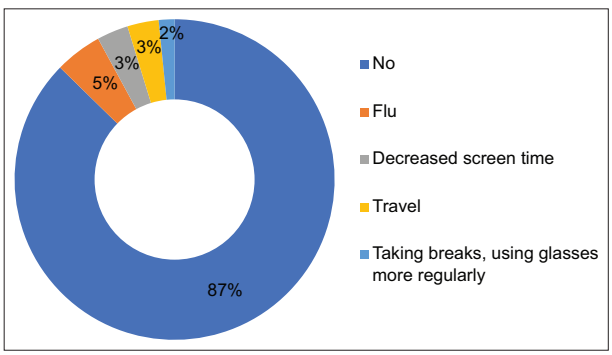

Figure 2: Description of the change in daily activities

The use of eye drops was successful in 53 (84%) patients. Four out of the remaining 10 patients in which the eye

Table 2: Clinical description of the patients

	n	%
Clinical dry eye symptoms		
Mild	12	19.05
Moderate	41	65.08
Severe	8	12.70
No response	2	3.17
Total	63	100.00
Assumed etiology		
Allergy	22	34.92
Eye surgery	13	20.63
Computer vision	6	9.52
Medications	4	6.35
Cancer	3	4.76
Age related	2	3.17
Rheumatoid arthritis	2	3.17
Ankylosing spondylitis	1	1.59
Avascular necrosis hip	1	1.59
Hypothyroidism	1	1.59
Osteoarthritis	1	1.59
Sjogren's syndrome	1	1.59
Nil	6	9.52
Total	63	100.00
Systemic conditions		
Hypertension	27	42.86
Diabetes mellitus	16	25.40
Coronary artery disease	5	7.94
Cancer	2	3.17
Ankylosing spondylitis	1	1.59
Depression	1	1.59
Dysfunctional uterine bleeding	1	1.59
Stroke	1	1.59
Nil	27	42.86

drop administration was not successful accepted to try the administration of eye drops after 3 weeks, whereas five patients were not sure about it. One patient refused to try the eye drop again after 3 weeks. 41.27% of the patients did not face any challenges while using the eye drops whereas an equal proportion of the patients said that there was too much hassle during administration of the eye drops. Other challenges faced were forgetfulness (96.35%), difficulty in handling the bottle of eye drops (4.76%), unable to find the bottles (3.17%), eye pain (1.59%), and sticky drops (1.59%) [Table 3].

All except three out of the 63 respondents said that it would be significantly easier if both eye drops were in one bottle.

Table 3: Description of success in using different types of eye drops and challenges faced while using them

	n	%
Successful use of drops		
No	10	15.87
Yes	53	84.13
Total	63	100.00
If did not succeed, shall we try again for another 3 weeks?		
Not sure	5	50
Yes	4	40
No	1	10
Total	10	100.00
Challenges while using the eye drops		
Nothing	26	41.27
Too much hassle	26	41.27
Forgot	4	6.35
One of the drops was difficult	3	4.76
Could not find the bottles	2	3.17
Increase pain and itching with new eye drops	1	1.59
Sticky drops	1	1.59
Total	63	100.00

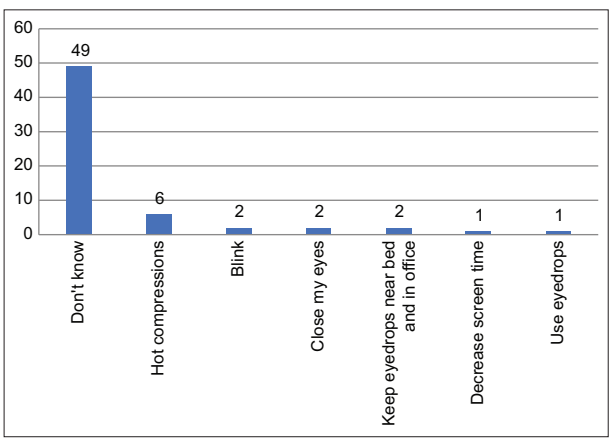

Figure 3: Description of tricks to relieve eye symptoms

On asking the patients about tricks to relieve eye symptoms, six patients mentioned hot compressions, whereas two patients each mentioned blinking their eyes, closing their eyes, or keeping the eye drops nearby whereas one patient mentioned reduced screen time [Figure 3].

Table 4 shows the comparison of the various independent variables based on the types of eye drops used. The patients with the highest mean age (67 years) belonged to the PEG group out of which one patient was between 41 and 55 years of age whereas two patients were of the age group of 71 years and above. In the CMC 0.5%, CMC 1%, and HPMC groups, the patients were

Table 4: Comparison of the features based on the type of eye drop used

	CMC 0.5%	CMC 1%	HPMC	Hyaluronate	PEG
Age in years (Mean±SD)	49.5±18.7	59.8±5.7	45.9±18.3	54.1±15.2	67±10.3
Age Group (years)					
18-25	3 (10.3)	-	2 (20)	1 (7.1)	-
26-40	9 (31)	-	2 (20)	2 (14.3)	-
41-55	6 (20.7)	2 (28.6)	2 (20)	3 (21.4)	1 (33.3)
56-70	6 (20.7)	4 (57.1)	4 (40)	6 (42.9)	-
71 and above	5 (17.2)	1 (14.3)	-	2 (14.3)	2 (66.7)
Gender					
Female	15 (51.7)	4 (57.1)	8 (80)	9 (64.3)	3 (100)
Male	14 (48.3)	3 (42.9)	2 (20)	5 (35.7)	-
Clinical dry eye symptoms					
Mild	5 (17.2)	3 (42.9)	2 (20)	2 (14.3)	
Moderate	21 (72.4)	4 (57.1)	8 (80)	7 (50)	2 (66.7)
Severe	3 (10.3)	-	-	4 (28.7)	1 (33.3)
Successful use of drops					
No	10 (34.5)	-	-	-	-
Yes	19 (65.5)	7 (100)	10 (100)	14 (100)	3 (100)
Challenges faced while using drops.					
Could not find the bottles	1 (3.4)	-	-	1 (7.1)	-
Forgot	2 (6.9)	-	-	2 (14.3)	-
Increase pain and itching with new eye drops	1 (3.4)	-	-	-	-
Nothing	9 (31)	4 (57.1)	5 (50)	6 (42.9)	2 (66.7)
One of the drops was difficult	3 (10.3)	-	-	-	-
Stickly used to drops	-	-	-	1 (7.1)	-
Too much hassle	13 (44.8)	3 (42.9)	5 (50)	4 (28.6)	1 (33.3)
Did the new way help more/was there a difference between the eyes?					
Could not really tell	3 (10.3)	-	-	1 (25)	-
No	9 (31)	4 (57.1)	6 (60)	3 (75)	-
Yes	17 (58.7)	3 (42.9)	4 (40)	-	3 (100)
Will you continue using the drops the new way?					
No	11 (37.9)	4 (57.1)	5 (50)	3 (21.4)	-
Not sure	2 (6.9)	-	-	-	1 (33.3)
Only if symptoms get worse	9 (31)	-	1 (10)	2 (14.3)	
Yes	7 (24.1)	3 (42.9)	4 (40)	9 (64.3)	2 (66.7)

distributed among almost all the age groups. All the patients who were administered PEG were females (100%) followed by those who were administered HPMC (80%), hyaluronate (64.3%), CMC 1% (57.1%), and CMC 0.5% (51.7%). Out of the patients who had moderate eye symptoms, the majority were administered HPMC (80%), followed by CMC 0.5% (72.4%) and CMC 1% (57.1%). Among the different eye drops used, successful administration was seen in all except CMC 0.5% (65.5%). Among the challenges faced, most of the patients reported too much hassle while using HPMC (50%), followed by CMC 0.5% (44.8%) and CMC 1% (42.9%). All the patients who were given PEG reported a difference in their symptoms, followed by CMC 0.5% (58.7%) despite the challenges faced while using the latter eye drop.

Discussion

The TFOS DEWS II report defines DED as "ocular surface disease characterized by a loss of homeostasis of the tear film,

and accompanied by ocular signs, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1] DED may cause ocular pain, fatigue, and vision disturbances, all of which have a deleterious effect on the quality of life of patients. The armamentarium for the treatment of dry eyes is as diverse as its presentation. Of the various available therapeutic strategies, the topical administration of tear substitutes or artificial tears has been the safest approach. The clinician can choose from several artificial tears.[5,6]

Viscosity-enhancing agents help DED by increasing the tear film integrity and retention time. They increase the tear film thickness because they are hygroscopic and may also protect the corneal epithelium by barrier function. These include sodium CMC, HPMC, carbomer, hyaluronic acid (HA), polyvinyl alcohol, povidone, dextran, and hydroxypropyl-guar (HP-guar). Viscosity-enhancing agents are also mucoadhesive and mucomimetic, while some tear supplements may also decrease tear evaporation by restoring the lipid layer of the tear film. Hypo-osmotic products help reduce the osmolarity of the tear film, increasing patient comfort. These also may counteract the proinflammatory nature of the high osmolarity tear film. Products with higher colloidal osmolarity, on the other hand, restore appropriate osmotic gradient and transport across ocular membranes. Compatible solutes, including glycerine and levocarnitine, are taken up by ocular epithelial cells to increase intracellular osmolarity.[7-11]

The optimum viscosity of the lubricating eye drop, therefore, is typically a balance between comfort and visual needs. While higher viscosity extends drop retention in the eye, it may cause optical aberrations. In addition, eye drops with greater viscosity may get crystallized on eyelids and lashes. It may therefore be better to use low-viscosity drops during the day, reserving thicker formulations such as ointments and gels for application at bedtime.[12-14]

In our study, we found that pre-treatment with a low-viscosity lubricating eye drop, followed by the more viscous eye drop, increased patient comfort in 59%, 43%, 40%, and 100% of the patients on CMC 0.5%, CMC 1%, HPMC, and hyaluronate and polyethylene glycol, respectively. Overall, 27 out of 53 (51%) eyes reported a significant improvement in comfort. Twenty-two (41.5%) patients reported that there was no significant improvement in their eyes, whereas four patients were unable to tell the difference. Ten out of 63 patients reported that they were unable to use the drops as suggested.

Of these, 25 (41.27%) patients said that they would continue to use the drop as prescribed, and 12 patients reported that they would do so only if symptoms worsened. Three patients were not sure if they would continue to use the two drops in sequence whereas 23 patients did not want to use the eye drops as prescribed.

Twenty-six (49%) patients reported that the use of the second drop was a challenge because it was too much hassle, an equal number of patients (26, 49%) reported that they had no difficulty in using the two drops sequentially. Two patients could not find the bottles, whereas four patients forgot. Other challenges faced were forgetfulness (96.35%), difficulty in handling the bottle of eye drops (4.76%), unable to find the bottles (3.17%), eye pain (1.59%), and sticky drops (1.59%).

Most patients are non-adherent to their medicine half the time, and this includes those with life-threatening diseases. While non-adherence is attributed to lack of access or forgetfulness, it may even be an intentional choice made by the patient, beyond the cost and complexity of the treatment regimen.[15-17]

Uchino *et al*. reported[18] that 10.2% of participants used eye drops at the specified frequency and that only 18.3% of participants knew the prescribed frequency for eye drops for dry eye treatment. The respondents used eye drops only when they had symptoms (61.3%). More than 50% reported that they forgot to use or carry the eye drops with them or that the eye drops were too cumbersome to carry. The latter may be more important in younger patients, who are busier and that may adversely affect instillation behavior.

Michaelov *et al*.[19] evaluated the barriers to adherence in Sjogren's syndrome, a more form a DED, and reported that the most important barriers to adherence were the cost of therapy (36.1%), forgetting eye drops (32.4%), difficulty in using the drops (20.5%), inconvenience (14.8%), and side effects (11.5%).

In our study, most of the patients (95.2%, 60 out of 63 respondents) said that it would be much easier to use the eye drops if both eye drops were in one bottle. Other authors have also reported that fixed-dose combinations decrease the incidence of non-compliance and should be considered in patients with chronic conditions, both systemically[20] and for eye drops.[21,22] In the case of eye drops, fixed combination treatments reduce the washout effect and exposure to preservatives and improve compliance by reducing schedule complexity.[22] That said, practitioners must be mindful when using fixed drug combinations for DED, for its ingredients, safety and efficacy profile of constituents, and need for their use.[23]

However, in our R-n-T protocol, we found that most of the study subjects (95%) would prefer both eye drops in one single container, even for the sequential administration of the eye drops.

On asking the patients about tricks to relieve dry eye symptoms, six patients mentioned hot compressions, whereas two patients each mentioned blinking their eyes, closing their eyes, or keeping the eye drops nearby and one patient mentioned reduced screen time. This indicates that their knowledge about lifestyle changes that may alleviate dry eye symptoms is deficient. It is of course imperative to make patient education an integral part of DED management. Both before and during treatment, patients must be apprised of lifestyle changes that help DED. Moreover, patient awareness helps manage expectations with respect to both, efficacy and tolerability of the prescribed treatment regimen and therefore may optimize adherence.[24]

Conclusion

While the initial results of the R-n-T protocol are equivocal, further studies with a larger sample size and grouping of patients

as per severity of DED as well as objective evaluation of the change in same are required. This will help in deciding the true value of sequential administration of lubricating eye drops.

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