Contact Lens Discomfort Management: Outcomes of Common Interventions

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ABSTRACT

Purpose: to assess the consecutive implementation of habitual contact lens discomfort (CLD) management strategies: lid hygiene, daily disposable contact lens (DDCL) fitting and artificial tear (AT) supplementation.

Methods: contact lens (CL) wearers with CLD symptoms (CLDEQ-8≥12 points) were included in the study. Subjects with Meibomian gland dysfunction (MGD) were instructed to perform lid hygiene. All participants were fitted with a DDCL (delefilcon A) and evaluated one month later. After, half of them were randomly assigned to use AT (Povidone-2%) at least three times/day, and all participants were evaluated one month later. Tests performed were: lower tear meniscus area (LTMA), bulbar, limbal and tarsal hyperaemia, non-invasive tear break-up time (NITBUT), and corneal and conjunctival staining. Weighted combined clinical scores (CS) were created to analyse signs. Changes in symptoms (CLDEQ-8) and CS were analysed using linear mixed models.

Results: Forty-two subjects (mean age: 23.2±4.9 years) completed the study. Two CS were created, CS-1 was composed of bulbar, limbal and tarsal hyperaemia and corneal staining, and CS-2 by NITBUT, LTMA and conjunctival staining. CLDEQ-8 was reduced after lid hygiene (mean: -2.73±2.13; p=0.012) and DDCL use (mean: -10.1±3.54; p<0.01), but not after AT use (p=0.62). CS-1 did not change after any intervention. CS-2 was higher (p=0.04) in DGM subjects after lid hygiene, it decreased (p=0.04) after DDCL use.

Conclusions: Lid hygiene is effective for reducing CLD symptoms in MGD patients. Refitting subjects with delefilcon A is an effective intervention for CLD

to reduce symptoms and achieve a healthier ocular surface. Simultaneous administration of AT did not further improve CLD.

Keywords: contact lens discomfort, daily disposable contact lenses, artificial tears, combined clinical score, CLDEQ-8.

Currently the contact lens (CL) market is growing slowly. In 2018, almost one-third of CL fits were new fits,[1] similar to the number of wearers discontinuing annually from CL wear.[2,3] CL discomfort (CLD) is a common condition affecting between 30% and 50% of CL wearers, which can eventually lead to CL drop out.[4] CLD can be associated with two factors, the CL characteristics (material, design, fit and lens care) and the environment (comprised by inherent and modifiable patient factors, and ocular and external environment).[5] Before attributing the CLD symptoms to the CL itself, the presence of coexisting anomalies that are potentially responsible for the patient's symptoms should be first discounted.[6] Meibomian gland dysfunction (MGD) is a condition that can contribute to CLD,[7] with a prevalence among CL wearers between 14% and 37%.[8,9,10] Lid hygiene is regarded as the mainstay of the clinical management of MGD.[11] Therefore, it should be considered when consulting with symptomatic CL wearers.

Regarding the CL associated factors contributing to CLD, switching lens materials or changing wear modality can improve the condition.[12] The first and most common step to solve CLD would be to refit the patient with a different CL.[13,14] It is known that DDCL reduces deposit accumulation, enhances comfort, visual quality, and decreases the risk of ocular infection.[15] Furthermore, wearing new lenses every day avoids the use of cleaning/storing chemicals.[16] Also, switching lens material to silicone hydrogel lenses could reduce dryness symptoms among some CL wearers.[17] Another way to ameliorate CLD problems could be to use topical lubricants. Some authors have demonstrated that tear supplements and wetting agents can be also helpful in CLD management.[17]

Different approaches to CLD management have been evaluated individually in various studies.[18,19,20] However, little is known about the summative effect of

these solutions on improving the condition, which is the common practice followed in daily clinical setting.

Also, clinical signs have been demonstrated to be poorly correlated with symptoms in CLD.[21] In fact, for subjective assessments, the most common instruments are questionnaires able to provide a single final score, which usually is the combination of several items. In the case of clinical assessments, clinicians can perform a wide range of clinical tests. However, there is no one single common sign present in all CL wearers suffering CLD.[22] Therefore, a set of tests combining several clinical assessments (i.e. a combined clinical score) may be more predictive for CLD than a single diagnostic test.[23,24]

The primary purpose of this study was to assess the consecutive implementation of habitual CLD management strategies, such as lid hygiene, DDCL fitting and artificial tears (AT) supplementation, similar to daily clinical practice, using a questionnaire and a combined clinical score.

METHODS

This study is a single-centre, open-label, prospective randomised design; it was approved by the East Valladolid Health Area Ethics Committee (Valladolid, Spain) and in compliance with the Tenets of the Declaration of Helsinki. The nature of the research and protocols were explained to the subjects, and written consent was obtained before entering the study.

Subjects and study visits

CL wearers who met the following inclusion criteria were invited to join the study: between 18 and 40 years old, contact lens dry eye questionnaire (CLDEQ)-

8 score ≥ 12,[25] astigmatism ≤ 0.75 D, and visual acuity ≤ 0.0 LogMAR. CL wearers had to have been CL users for at least 6 months before being included in the study. Additionally, subjects had to wear their CLs at least 2 days per week for 4 hours a day. Exclusion criteria were extended or continuous CL wear (overnight use), current use of the DDCL used in the study (study-DDCL: delefilcon A) and dry eye disease patients. Dry eye disease was defined as an Ocular Surface Disease Index (OSDI) score ≥13[26] and at least two of the following tests altered (in at least one eye): fluorescein tear break-up time ≤7 seconds, fluorescein corneal staining extent ≥grade 2 (CCLRU scale)[27] in any of the corneal areas, and Schirmer I test without anaesthesia ≤ 5 mm. Subjects with level ≥3 of MGD according to the MGD workshop classification were also excluded.[28] Those volunteers who had any other active ocular disease, ocular allergy, history of anterior ocular surgery, any systemic disease that contraindicated CL wear, and/or used any topical medication other than AT were also excluded.

The study protocol was designed based on the common practice followed in the daily clinical setting and consisted of four visits: a screening visit, a baseline visit and 2 follow-up visits separated one month.

Screening visit: All subjects were instructed not to wear their CLs for at least 24 hours before the screening visit. Clinical evaluation was performed (see section Clinical Evaluation). After eligibility was confirmed, subjects underwent MGD assessment (see section Clinical Evaluation). Those who were diagnosed with MGD were instructed to perform lid hygiene 1 month before starting the study (baseline visit) and throughout the whole study. Only patients suffering from level 1 (subclinical) or 2 (symptomatic minimal) of MGD according to the MGD workshop classification[28] were recruited. Cotton discs and eyelid wipes (Systane

Eyelid Cleansing Wipes; Alcon Laboratories, Inc., Fort Worth, Texas, USA) were provided. Instructions were also given on how to perform lid hygiene properly. The instructions consisted of applying warm compresses over 5 minutes (a cotton disk wetted with warm water), followed by a gentle massage of the upper and lower lids, and finally, eyelid wipes.[11]

Baseline visit (V0): This visit was scheduled one week after the screening visit, except for those subjects diagnosed with level 1 or 2 MGD that were scheduled one month after the screening visit. All subjects wore their current CL for at least 4 to 6 hours. During the visit, a clinical evaluation was performed (see Clinical Evaluation). The MGD condition was also assessed during all the visits (baseline and follow-up visits). At the end of this visit, subjects were provided with the study-DDCL for a month (delefilcon A, DAILIES TOTAL1®; Alcon Laboratories, Inc., Fort Worth, Texas, USA). They were instructed to use them at least as much as they were using their habitual CL.

Visit 1 (V1): This visit was scheduled one month after V0. All subjects wore the study-DDCL for at least 4 to 6 hours. During the visit, clinical evaluation was performed (see section: Clinical Evaluation). At the end of this visit, the same DDCL was provided for another month, and half of the subjects were also randomly dispensed povidone 2% preservative-free eye drops (Filmabak, Thea, Clermont-Ferrand, France). They were instructed to use the AT at least three times each day, after CL insertion, in the middle of the day and after removing the CL. The other half of participants that did not received AT were instructed not to use any other AT or lubricants.

Visit 2 (V2): This visit was scheduled one month after V1. All subjects wore the study-DDCL for at least 4 to 6 hours, and they were asked not to use AT at least one hour before the visit. During the visit, clinical evaluation was performed (see section Clinical Evaluation).

At each visit, compliance with the CLD intervention was evaluated using direct questions about their CL use routine.

The study design is shown in figure 1.

Clinical evaluation

Symptoms evaluation

Symptoms of discomfort were quantified by administering the CLDEQ-8. CL wearers were instructed to complete the questionnaire considering the symptoms they had commonly suffered in the past 2 weeks while wearing the CL. The CLDEQ-8 total score ranges from 1 to 37, with a diagnostic cut-off of ≥12 points. A clinically important difference is ±3 points.[25]

Clinical signs

A Topcon 3D OCT 2000 (Topcon Corporation, Tokyo, Japan) was used to measure the lower tear meniscus area (LTMA). The “polygon selections” tool of the ImageJ software (http://imagej.nih.gov/ij/) was then used to draw the tear meniscus perimeter from the scanned images and calculate the LTMA in μm^2.[29] Non-invasive tear break-up time (NITBUT) was evaluated using Tearscope plus (Keeler, Windsor, UK) (http://www.keeler.co.uk/). The mean of the three measurements of the NITBUT was calculated. Then, the ocular surface was

examined with a slit lamp (SL-D7; Topcon Corporation, Japan) (http://global.topcon.com/). Bulbar and limbal hyperaemia were graded using the Efron grading scale (0-4, in 1-unit steps),[30] while tarsal hyperaemia was graded using the CCLRU grading scale (0-4, in 1-unit steps).[27] Sodium fluorescein (BioFluoro, Tiedra farmacéutica S.L, Madrid, Spain) was instilled, and corneal staining was evaluated using the cobalt blue and the Wratten #12 yellow filters (http://www.kodak.de/ek/DE/de/corp/default.htm). The extent of corneal staining was assessed using the CCLRU grading scale (0-4). Finally, lissamine green (I-DEW green Entod Research Cell, UK Ltd. Tottenham, Ln, London, UK) was instilled, and conjunctival staining was evaluated using the CCLRU grading scale (0-4, in 1-unit steps).

In order to detect MGD, lid margin and lipid secretion were evaluated. First, lid margin was scored using a 0-4 scale based on the presence (1) or absence (0) of each of these 4 criteria, irregular lid margin, vascular engorgement, plugging of meibomian gland orifices, and shift of the mucocutaneous junction.[31] All points from each sign were summed, thus the maximum score could be 4. Second, quality and expressibility of lipid secretion was evaluated applying digital pressure through the substance of the lids, and it was assessed on a 0-3 scale: 0= clear meibum, easily expressed; 1= cloudy meibum, easily expressed; 2= cloudy meibum expressed with moderate pressure; 3= meibum not expressible, even with hard pressure.[32]

Clinical evaluation was performed in both eyes, however, only the outcomes corresponding to one eye were computed for analysis. The most symptomatic eye was chosen, according to the opinion of the participant, if both eyes were similar, the study eye was selected using a random table.

Statistical analysis

Sample size calculation

The sample size was calculated considering a significance level of 0.05 and a statistical power of 0.8. It was determined based on a 2.5 odds-ratio of CL wearers reassigned into the asymptomatic group (CLDEQ-8<12 points) by the end of the study. Thus, the resulting sample size was 47 CL wearers, with an expected drop-out rate of 10%.

Development of combined clinical scores

To analyse clinical tests results, a weighted combined clinical score was built. This combined clinical score was created using the 7 clinical tests performed in the screening and follow-up visits to assess the ocular surface (bulbar, limbal and tarsal hyperaemia, NITBUT, LTMA, and corneal and conjunctival staining). The goal was to group all the variables in a single clinical score following statistical criteria.

Firstly, variables were divided as either quantitative or ordinal, and a correlation matrix was performed to observe how the variables correlated with each other. For quantitative variables, Pearson's correlation coefficient was used, and for ordinal variables, Spearman's correlation coefficient was selected. Secondly, to create a model for the latent variable called Clinical Score, structural equation models were used. The purpose of structural equation models was to assess unobservable latent variables or factors based on one or more observed variables. Firstly, the number of factors (groups of variables) defining the Clinical Score was determined using the Horn parallel analysis,[33] the Velicer´s Minimum Average Partial,[34] the Very Simple Structure,[35] and the Item Hierarchical

Clustering Algorithm.[36] For the clustering algorithm, each variable was added to a cluster if it improved the cluster reliability. Reliability was measured with the Cronbach α and Revelle β. For this analysis, the R package psych was used.[37] Once the initial model was established, it was fitted using structural equation models with a robust maximum likelihood estimation method. Different parameters were added or deleted to improve the goodness of fit based on modification indexes. The goodness of fit was evaluated by the Chi-square test, root mean square error of approximation, comparative fix index and non-normed fit index. Finally, the normality of distribution of any residuals was checked for all models. Logarithmic transformation (base 2) was applied when the normality assumption was not valid.

Effect of CLD interventions

Subjective (CLDEQ-8 outcomes) and Clinical Scores were used to evaluate the possible changes observed after undergoing consecutive CLD management strategies. Linear mixed models were fitted (R package nlme)[38] to evaluate the effect of each intervention on both scores, providing an appropriate framework for studying the relation between the responses of the subjective and objective scores (dependent variables) and the different interventions performed (independent variables). It allowed us to analyse repeated measurements made on the same participant (longitudinal study) and incorporating random effects and fixed effects. The scores were quantified, estimating the least-square means, and then, post-hoc comparisons were performed. A multivariate-t adjustment was used for multiple comparisons (R package Estimated Marginal Means).[39] Continuous variables are presented as mean± standard deviation and categorical variables are presented as median [interquartile range].

Statistical analyses were conducted using the statistical package for the social sciences software (SPSS 22.0 for Windows) and the R statistical software (version 3.1.1, Foundation for statistical computing, Vienna, Austria).[40]

RESULTS

A total of 47 CL wearers were recruited, with 42 subjects finishing the study. There were 5 drop-outs due to travel and scheduling constraints. Demographic data, CL characteristics, wearing habits, and results of the seven clinical tests in the screening visits for the 42 CL wearers are summarised in Table 1. Further characteristics of the CL used by subjects before recruitment are detailed in Supplemental Digital Content (Table S1). CLDEQ-8 scores and Clinical Scores obtained during the screening, baseline and the 2 follow-up visits are provided as Supplemental Digital Content (Tables S2, S3 and S4).

In the screening visit 11 subjects were diagnosed with MGD, therefore, they performed lid hygiene for the whole study. In V0, all the subjects (n=42) were fitted with the study-DDCL. Then, in V1, 21 randomly allocated CL wearers used AT. All the subjects who underwent V0 finished the study.

Development of the Clinical Scores

According to the Horn parallel analysis and the Very Simple Structure test, a model with two factors of the latent variables was determined. Contrastingly, the Velicer´s minimum average partial and the Item hierarchical clustering algorithm proposed a one single factor model. Both models were adjusted using structural equation models to choose the most consistent, which was the model with two factors (two Clinical Scores). The likelihood-ratio test and goodness of fit of the

Clinical Scores are detailed in Table S5.1 and Table S5.2 of the Supplemental Digital Content. Therefore, two Clinical Scores were obtained (Figure 2). The first one (Clinical Score 1) was the weighted combination of the following variables: limbal, bulbar, and tarsal hyperaemia and corneal staining. Clinical Score 2 was the weighted combination of conjunctival staining, NITBUT and LTMA. A 0 score value for both Clinical Scores reflected a healthier clinical condition, while a 100 score value reflected poorer clinical condition.

For Clinical Score 2, a logarithmic transformation was performed because the residuals of the model showed a lack of normality. Thus, outcomes are detailed as fold changes.

Effect of CLD interventions

Lid hygiene effect

From the initial 11 CL wearers detected with level 1 or 2 of DGM during the screening visit, only 4 remained having MGD (2 with level 2 and 2 with level 1) at the end of the study. Results of lid margin status and lipid secretion during the study are provided as Supplemental Digital Content (Table S6).

Evolution of symptoms as measured with the CLDEQ-8 and Clinical Scores after lid hygiene are presented in table 2. Participants who underwent lid hygiene showed a significant ($p=0.012$) higher decrease on CLDEQ-8 score. After performing lid hygiene, no significant change was found in Clinical Score 1, however, Clinical Score 2 was significantly ($p=0.04$) higher in MGD participants.

242 DDCL effect

243 The effects of the DDCL fitting on the CLDEQ-8 and Clinical Scores are
244 presented in table 3. Regarding the efficaciousness of fitting the study-DDCL,
245 there was a significant (p<0.0001) decrease on the CLDEQ-8 after the first month
246 using the study-DDCL (Table 3, 1-month Study-DDCL wear effect). However,
247 CLDEQ-8 was not significantly (p=0.40) further reduced after the second month
248 of study-DDCL wear (Table 3, 2-month Study-DDCL wear effect). Additionally,
249 we observed that the improvement in CLDEQ-8 scores was not significantly
250 (p=0.68) different between previous monthly and daily CL wearers (Table 3,
251 replacement frequency change effect).

252 We did not find any significant (p=0.75) change in the Clinical Score 1 after
253 one or two months of study-DDCL (Table 3). Likewise, we did not find any
254 difference (p=0.42) in the change of Clinical Score 1 between previous monthly
255 or daily CL users. There was a significant (p=0.04) decrease in Clinical Score 2
256 (towards a healthier ocular surface) after one month wearing the study-DDCL
257 (Table 3: score decreased 1.35 (1/0.74) times in V1). In contrast, there were no
258 significant differences in Clinical Score 2 neither after the second month wearing
259 the study-DDCL (p=0.98), nor between previous monthly and daily CL wearers
260 (p=0.12).

261 Artificial tears effect

262 The effects of the AT use on the CLDEQ-8 and Clinical Scores are presented
263 in table 4. There were not significant ($p \geq 0.09$) differences in the CLDEQ-8 scores
264 or in the clinical scores between the group who used the AT and the group who
265 did not.

CLDEQ-8 classification

According to the CLDEQ-8 classification, none of the CL wearers that performed lid hygiene became categorized as asymptomatic (CLDEQ-8 score<12 points). After fitting the study-DDCL, 20 out of 42 (47.61%) CL wearers became categorized as asymptomatic (Figure 3. All subjects V1). After additionally using AT, 5 (4 of the AT group and 1 of the no AT group) out of the 22 subjects that remained classified as symptomatic became categorized as asymptomatic

In summary, at the end of the study, from the 42 CL symptomatic wearers that entered the study, 25 (59.52%) finished classified as asymptomatic (Figure 3. All subjects V2). The CLDEQ-8 score at the beginning and the end of the study of these 25 CL wearers who became categorized as asymptomatic was 21.92±3.56 points (range: 15-29) and 6.60±3.40 (range: 1-11) ($p<0.001$), respectively. Regarding the subjects that remained symptomatic during the whole study (17 out of 42, 40.48%), their mean CLDEQ-8 score decreased also significantly ($p<0.001$) from 21.18±4.60 (range: 15-30) to 16.41±3.86 (range: 13-22).

DISCUSSION

CLD is a challenging condition, affecting the short- and long-term success of CL wear.[4] CL wearers solve these symptoms by reducing their daily wearing time or removing their CL either temporarily or permanently. However, some interventions can be used to manage the condition, such as lid hygiene, DDCL refitting and/or use of AT.[6] Several authors have proven the ability of these interventions to reduce CLD.[41,42,43] However, literature is scarce regarding the

summative effect of undergoing the most common CLD interventions consecutively, as it is performed in clinical settings.[13]

Our results showed that the sequential implementation of commonly used interventions in the clinical setting to manage CLD was effective in managing symptoms and signs. Up to 60% of subjects were finally classified as asymptomatic as measured with CLDEQ-8 and an improvement in ocular surface health after one month of study-DDCL wear was observed. In addition, we have observed that lid hygiene was an effective implementation to reduce MGD signs (Supplemental Digital Content). Around 50% of CL wearers with 1-2 level of MGD showed no further signs at the end of the study.

In this study, we used a validated questionnaire (CLDEQ-8) to evaluate CLD symptoms. Additionally, we also included the use of combined clinical scores to improve the analysis of clinical tests outcomes. There is a lack of consensus in the literature regarding the possible association between symptoms and clinical observations when wearing CL.[21,22,44] Consequently, we decided to combine the information obtained with several clinical tests creating a weighted combined clinical score. This newly-designed score could better detect the ocular surface changes observed in our sample of symptomatic CL wearers after undergoing different CLD interventions. Combined clinical scores have been used previously in other fields of the medicine such general surgery or obstetrics and gynecology.[45,46] In addition it has been also used in the evaluation of a treatment for corneal neovascularization,[47] and to our knowledge this is the first time that it is used for CLD research purposes. It must be taken into account that this is a statistical approach including the clinical tests evaluated in our study sample. Further research is needed to include other clinical tests that could be related

with CLD (such as the presence of lid wiper epitheliopathy or lid-parallel conjunctival folds, among others), and to validate this statistical approach.

In our study, the initial seven clinical tests were grouped into two combined clinical scores based on statistical analysis using structural equation models, thus, variables were not grouped following a clinical decision process. Clinical Score 1 gathered information regarding conjunctival (limbal, bulbar and tarsal) hyperaemia and corneal staining, and Clinical Score 2 included NITBUT, LTMA and conjunctival staining data. Clinical Score 2 was able to detect clinical changes when CL users underwent the CLD interventions performed in this study. Data gathered by this Clinical Score appeared to be more precise and might help to reduce the lack of correlation between subjective and clinical tests in CL wearers. As it provides a unique score that allows a more precise way to evaluate clinical changes, overcoming limitations encountered when monitoring multiple clinical test outcomes that may have conflicting results. However, due to the nature of the sample (habitual CL wearers) and the inclusion and exclusion criteria of the study, we were not able to find higher changes in clinical signs, since participants were normal subjects without moderate nor severe ocular surface alterations (Table 1). Subjects with more clinical signs, such as dry eye disease patients were not included since aetiology seems to be different from CLD,[4] however dry eye disease patients are prone to have CLD secondary to its ocular surface disease.[4] Thus, according to the exclusion criteria, only subjects with evaporative mild dry eye (MGD levels 1 and 2) could have participated in the study.

According to a dry eye report based on a survey performed in 2018 by eye care practitioners in the United States of America,[13] the majority of clinicians

(65%) classified most CL dry eye patients as the evaporative type. In addition, it has been previously estimated that up to 35% of symptomatic CL wearers presented MGD.[9] This study has been designed to evaluate the common interventions followed in daily clinical setting. Therefore, excluding MGD subjects could be not enough representative of the habitual clinical practice. In fact, 26.2% of our CL wearers recruited were diagnosed of mild MGD (Level 1 or 2), thus, our sample might be quite similar to the CL wearers who are consulting in the daily clinic. For this reason, the first stage in our study was to evaluate the Meibomian glands and recommend lid hygiene in CL wearers with level 1 or 2 MGD.[25] This first stage was performed to obtain a healthier ocular surface status in CL wearers with MGD prior to the baseline visit. Thus, we aimed to reduce the effect of uncontrolled ocular factors that could bias the outcomes of the other CLD interventions performed. In our study, it was observed that lid margin status improved after the lid hygiene (Table S6), outcomes that are similar to those reported by Guillon et al.[48] In addition, in our study it was observed that performing lid hygiene provided higher improvement in symptoms (Table 2). This improvement in symptoms has been also observed in the study of Paugh et al.[49] Regarding signs, in our study no change in Clinical Score 1 was observed between MGD and no MGD participants. However, Clinical Score 2 showed that MGD subjects did not improved so much as no MGD participants did. This difference observed in the Clinical Score 2 could have been observed because MGD participants had a less healthy ocular surface at the beginning of the study in comparison with no MGD participants.

As indicated in the 2018 dry eye report, 52% of the practitioners would refit their CLD patients into a different CL with a more frequent replacement schedule,

as the first-line recommendation in CLD management.[13] Indeed, 64% of the clinicians reported that DDCL based on silicone hydrogel materials were the most efficacious to reduce CLD.[13] Therefore, in this study, the first intervention was to refit CL wearers with a silicone hydrogel DDCL. However, the hydrophobic nature of silicone may also lead to poor wettability, and increase the lens surface coefficient of friction, which may contribute to discomfort with silicone hydrogel CL.[50,51] For this reason, we selected delefilcon A DDCL, because it has a very low silicon content[52] that can provide similar characteristics to both conventional hydrogel and silicone hydrogel lenses.[53] Also, delefilcon A has shown to provide longer NITBUT, and greater wettability than other silicone hydrogel DDCLs,[54] resulting in longer comfortable CL wear time compared to a conventional hydrogel DDCL.[42] Similar to these results, we found a significant improvement in CL symptoms, as measured with the CLDEQ-8, for both monthly and daily CL subjects when fitted with delefilcon A during the first month. A second month with this DDCL was also assessed to evaluate if further time using delefilcon A CL could improve even more symptoms and signs. However, the results obtained during the second month did not show any further improvement, thus, one month is enough to observe changes in the status of CLD after using this CL. These findings showed that changing the CL material into this material and/or the replacement frequency is effective for CLD symptoms management independently of the previous CL. In addition, the Clinical Score 2 (composed of conjunctival staining, NIBUT, and LTMA) decreased significantly when subjects were refitted with study-DDCL (Table 3).

The second most recommended intervention (11%) among practitioners for CLD subjects is AT.[13] Therefore, the next stage in our study was to evaluate the

use of AT in CLD. Tear substitutes were administrated to half of the subjects to evaluate the effect of study-DDCL and AT compared to the study-DDCL only. AT were administered to half of the subjects in a random order, independently of the CLDEQ-8 score to observe if the remaining symptoms could be decreased even further, as it has been showed before.[55–57] The AT selected in this study contained povidone 2%. It is a polymer that acts as a viscosity enhancer, and it can be used by CL wearers and non-wearers to alleviate dry eye symptoms.[58] The use of these preservative-free eye drops has been previously studied in CL wearers suffering from computer visual syndrome, showing a decrease of symptoms of ocular tiredness, dryness, and difficulty in focusing.[58] In contrast, our results showed no subjective (CLDEQ-8 score) or clinical (Clinical Scores 1 and 2) improvements after the use of povidone 2% AT. The absence of significant changes in our study may be because symptoms after wearing the study-DDCL for only one month may not be severe enough to show an improvement in CLD with using AT. Another explanation could be that the combination of the study-DDCL with this AT was not effective enough; other AT could provide better results.

Finally, we observed that from the 42 symptomatic CL wearers initially recruited, 25 ended the study classified as asymptomatic according to the CLDEQ-8 score criteria. We demonstrated that performing these consecutive CLD interventions could result in successful CLD management in at least 60% of CL wearers. The mean reduction of the CLDEQ-8 scores in this 25-group of CL wearers classified as asymptomatic at the end of the study was noteworthy (from 21.92±3.56 to 6.60±3.40 points), taking into account that a 3-point variation is considered to be a clinically important change.[25] Appropriate CLD management

414 could result in lower CL wear discontinuation, and therefore, lower CL dropout
415 rates. Around 40% of the subjects of the study remained symptomatic, however,
416 these CL users showed a clinically important reduction (from 21.18±4.60 to
417 16.41±3.86 points) in their symptoms as measured with the CLDEQ-8. Therefore,
418 the CLD interventions administered were not as effective in these CL wearers
419 regarding symptoms.

420 One of the limitations of this study is that the study-DDCL fitted, the AT
421 provided (povidone 2% preservative-free) or the order of both CLD interventions
422 might not be the best clinical approach. Moreover, there are other factors, such
423 as environmental factors, that have not been considered and could have affected
424 the outcomes obtained in our study. Therefore, despite our results show evidence
425 of effective CLD management after common interventions, they must be
426 interpreted with caution if different DDCL and AT are recommended in the daily
427 clinical setting. Another limitation of the present study concerns compliance. We
428 were not able to know whether the CL wearers recruited adequately performed
429 the lid hygiene or properly used the AT. Subjects were asked about their
430 compliance with our instructions, and the importance of a proper compliance was
431 stressed at each visit. Finally, we were not able to mask the study-DDCL blister,
432 therefore, subjects knew what DDCL they were fitted with. Additionally, we do not
433 know if any of the subjective outcomes could be biased, as the improvement that
434 subjects had when the study-DDCL was worn cannot be completely related to the
435 CL fitted itself, factors such as the fact of changing the CL could have affected
436 the results.

437 In conclusion, our study outcomes show that refitting symptomatic CL wearers
438 with delefilcon A DDCL is an effective intervention for CLD. Additionally,

439 performing other interventions not related to the CL itself, such as MGD
440 management could also improve CL comfort. However, administration of AT to
441 DDCL wearers did not appear to further improve CLD symptoms or signs.

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FIGURE LEGENDS

Figure 1. Flow chart of the study design. CL: contact lens; DDCL: daily disposable contact lens (delefilcon A); MGD: Meibomian gland dysfunction; w/wo: with/without. † After visit 2, half of the subjects started using artificial tears. These subjects were randomly allocated.

Figure 2. Clinical variables included in each Clinical Score. The numbers represent the relative weight of each variable within each Clinical Score. NITBUT: non-invasive tear break-up time; LTMA: lower tear meniscus area.

Figure 3. Percentage of symptomatic/asymptomatic contact lens wearers (based on the Contact Lens Dry Eye Questionnaire-8 score) after each contact lens discomfort intervention. V0/V1/V2: visit 0/1/2; Study-DDCL: daily disposable contact lens (delefilcon A).