Title

Intense Pulse Light combined with Low-level Light Therapy in Dry Eye Disease: A Systematic Review.

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ABSTRACT

Objectives: To evaluate the improvement in symptoms and signs associated with intense pulse light (IPL) combined with low-level light therapy (LLLT) in the treatment of dry eye disease (DED).

Methods: A systematic review of full-length original studies reporting the effects of IPL combined with LLLT for DED in two databases, PubMed and Scopus, was performed according to the PRISMA statement. The Quality Assessment Tool for case series studies from the National Heart, Lung, and Blood Institute was used to analyse the quality of the studies selected.

Results: The search provided a total of 393 articles, of which six were included. Significant decreases in the Ocular Surface Disease Index (OSDI) score, meibomian gland dysfunction (MGD) score, MGD grade and meiboscore and increases in tear film stability, lipid layer thickness (LLT) and loss area of the meibomian gland (LAMG) have been reported. Concerning tear volume, tear meniscus height (TMH) and Schirmer's test remained unchanged. In relation to tear osmolarity (OSM) and corneal fluorescein staining (CFS), contradictory outcomes were found.

Conclusions: IPL combined with LLLT for the treatment of dry eye improves OSDI, tear film stability and meibomian gland function; thus, this treatment may be recommended for DED patients due to MGD.

KEYWORDS

Intense pulse light—Low-level light therapy—Meibomian gland dysfunction—Dry eye disease.

INTRODUCTION

Intense pulsed light (IPL) is a form of light therapy that that uses flash lamps to emit noncoherent, polychromatic high-intensity light of determined wavelength spectrum, ranging from 500 to 1200 nm.[1,2] Using these wavelengths, the potentially harmful ultraviolet radiation, which occurs below 500 nm, is filtered.[3] IPL applications have been used for dermatological procedures such as hair removal, pigmented lesions, acne rosacea, psoriasis and skin photo rejuvenation.[1,4–8] IPL is considered a safe and effective treatment option with minimal adverse effects, which may include blistering and hypopigmentation of the skin.[9]

In 2002, Toyos et al. reported that patients with dry eye disease (DED) who received IPL treatment for rosacea, acne or other skin disorders reported improvements in their dry eye symptoms.[10] This finding led to the development of different IPL devices to specifically treat DED. Currently, different studies have shown that IPL is a safe and effective treatment that improves the signs and symptoms of patients with evaporative dry eye (EDE) owing to meibomian gland dysfunction (MGD).[10–14] The main mechanism of action of IPL is thermal. IPL energy absorbed by haemoglobin and Demodex's exoskeleton, which causes thrombosis of abnormal blood vessels and necrosis of demodex,[7,15,16] reduces the concentration of inflammatory and microbial mediators in the eyelid and meibomian glands, thus preventing their dysfunction and improving meibum flow.[17]

Low-level light therapy (LLLT) is a treatment used for dermatological purposes and is based on the principles of photobiomodulation.[18] This technique involves light-emitting diodes (LEDs) at wavelengths in the visible (390 to 700 nm) and near-infrared (780 to 1100 nm) spectral range that are absorbed by chromophores localized in the skin, inducing cellular photoactivation that is suggested to repair damaged cells and improve cellular function.[19,20] A novel application of LLLT is the treatment of patients with DED due to MGD. Park et al.[21] have shown that LLLT performed on the upper and lower eyelids improves the signs and symptoms of MGD in patients with minimal adverse effects. The mechanism of action of photobiomodulation in MGD is still unclear, but it is suggested that LLLT stimulates adenosine triphosphate (ATP) production in the meibomian glands, which leads to heating and promotes meibum flow.[20]

To date, some published studies have evaluated the efficacy of IPL combined with LLLT for DED by using the Eye-Light or Epi C-Plus device (Espansione Marketing S.p.A., Bologna, Italy), which perform these two treatments in each session.[22–28] However, to our knowledge, there is no systematic review exploring all the literature available on the topic of IPL combined with LLLT in the treatment of DED.

The objective of this systematic review is to describe the effects on symptoms and signs achieved with IPL combined consecutively with LLLT in DED in the available scientific literature.

METHODS

Data sources and search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[29,30] We identified 393 articles published before April 24, 2022, through the following databases: PubMed (208 studies) and Scopus (185 studies). The data search strategy with Boolean operators was as follows: (dry eye disease OR dry eye OR DED OR aqueous-deficient dry eye OR ADDE OR meibomian gland dysfunction OR MGD OR evaporative dry eye OR EDE) AND (intense pulse light OR intense pulse light therapy OR IPL OR low-level light therapy OR LLLT OR near-infrared light OR NIL OR infrared radiation). Additionally, the references of the retrieved articles were reviewed to identify other related studies if they met the inclusion criteria.

Study selection

After an initial screening, duplicate studies were removed by DistillerSR. The remaining studies underwent additional screening stages, which included title screening, abstract screening, and full-text screening. Studies unrelated to the topic were excluded from the review during title and abstract screening. Full-text studies without treatment with IPL combined with LLLT were also excluded from the review. These studies were reviewed by two investigators who selected them according to inclusion and exclusion criteria.

The inclusion criteria were as follows: human studies, full-length original articles and retrospective or prospective case series studies. The exclusion criteria included non-English publications, unindexed journals, and IPL treatment alone or combined with other treatments other than LLLT. There were no restrictions placed on the country in which the study was performed, the follow-up period and the sample size or results of the studies.

Quality assessment and data extraction

The data from each study were collected and summarized independently in tables designed by two researchers. The following information was obtained from each of the articles: (1) author and date of publication (year), (2) study design, (3) mean follow-up of all patients in the whole procedure (expressed in months), (4) number of patients, (5) number of eyes involved, (6) mean age of the patients (expressed in years), (7) patients' sex (male/female), (8) type of DED, (9) light therapy treatment, and (10) light therapy device. Regarding the results of the studies, the following date were collected: (11) Ocular Surface Disease Index (OSDI), (12) Non-Invasive Break-Up Time [NIBUT, expressed in seconds (s)], (13) Break-Up Time [BUT, expressed in seconds (s)], (14) Tear Meniscus Height [TMH, expressed in millimetres (mm)], (15) Osmolarity (OSM, expressed in mOsm/L), (16) Schirmer's test [ST, expressed in millimetres (mm)], (17) Corneal Fluorescein Staining (CFS), (18) Lipid Layer thickness [LLT, expressed in nanometres (nm)], (19) MGD score (Grading scale for MGD with a score of 0-15), (20) MGD grade (Grading scale for MGD with a grade of 0 to 4, where grade 0 is normal meibum, grade 1 is turbid oil, grade 2 is turbid and viscous oil appearance, grade 3 is "ropy" meibum and grade 4 is no expression), (21) Meiboscore (Grading system for quantifying the loss of meibomian gland area with a score of 0-6), (22) Loss Area of Meibomian Gland [LAMG expressed in percentage (%]) and finally (23) authors opinion expressed by commenting in favour of light therapy treatment in DED.

The literature that remained after full-text screening was examined to assess the quality of the studies. To avoid the risk of bias, two dependable authors created a synopsis table (supplemental table 1) based on the Quality Assessment Tool for Case Series Studies from the National Heart, Lung, and Blood Institute.[31] A third nonblinded assessor decided the quality of the studies when disagreements occurred between the two assessors. This assessment did not determine the exclusion of any study. Please refer to supplemental table of the quality assessment of the studies included in this systematic review to avoid the risk of bias in Supplemental Digital Content 1.

RESULTS

Search results

The study selection process of this systematic review is presented with a flowchart diagram in Figure 1. The initial search resulted in 393 studies from two electronic databases. A total of 273 studies remained, and they were additionally screened after duplicate studies were removed. A total of 245 articles were

excluded through title and abstract screening. During full-text screening, the remaining 28 studies were reviewed, and 22 studies were removed because they included IPL treatment without LLLT (20 studies), they were non-English publications (1 study), and they were letters to the editor (1 study). Finally, six studies were included in this systematic review.[22–25,27,28]

Study characteristics

Detailed study characteristics are presented in Table 2. The design of the included studies was a series of cases published between 2019 and 2021. We studied 990 eyes from 495 patients with a mean age of 59.3 ± 6.6 years. The sex distribution was 337 females (75.2%) and 111 males (24.8%). Patient follow-up, expressed in months, ranged from 0.2 months [28] to 15 months [27] with a mean follow-up of 5.5 ± 5.11 months. Regarding DED distribution, five studies reported EDE owing to MGD,[22,24,25,27,28] and 1 study reported mixed dry eye (MDE) due to Sjögren's Syndrome Dry Eye (SSDE) combined with MGD.[23] Regarding light therapy treatment, all included studies combined IPL with LLLT. Regarding the light therapy device, five studies [23–25,27,28] utilized Eye-light, and one study [22] utilized Epi C-Plus. Two studies [22,27] had conflicts of interest by the authors.

Outcomes

An evaluation of DED symptom and signs is presented in Table 3. Symptom outcomes were evaluated with the Ocular Surface Disease Index OSDI score. All included studies evaluated OSDI score, and it was significantly improved in all studies.

The signs outcomes were evaluated with NIBUT, BUT, TMH, OSM, ST, CFS, LLT, MGD scores, Meiboscore, MGD grade, and LAMG. Tear film break up time was examined in all studies included. Two studies [25,27] evaluated NIBUT and 4 studies [22–24,28] evaluated BUT. Concerning NIBUT, one study [25] showed a little, nonsignificant worsening. However, the other study [27] obtained a significant improvement with a previous and subsequent value of 4.3 s and 7.3 s, respectively. BUT was significantly improved in all studies. TMH and OSM were measured in two studies.[25,27] THM remained unchanged in one study,[25] while it had a little, nonsignificant improvement in the other study.[27] OSM was significantly worsened in one study [25] with a previous and subsequent value of 98.1 and 315.5 mOsm/L, respectively. However, it was significantly improved in the other study,[27] obtaining a previous and subsequent value of 319.2 to 304.3 mOsm/L, respectively. ST was assessed in four studies,[23–25,28] remained unchanged in two studies,[23,24] had a little, nonsignificant improvement in one study [28] and a significant improvement in one study [25] with a

previous and subsequent value of 9.6 to 11.4 mm, respectively. CFS was examined in two studies.[25,28] CFS was significantly improved in one study [25] with a previous and subsequent CFS of 51.6 to 45.2%, respectively. However, it remained unchanged in the other study.[28] LLT was only measured in one study,[25] which was significantly improved with a previous and subsequent LLT of 47.4 to 73.9 nm, respectively. The MGD score and Meiboscore were evaluated in one study,[28] and they were significantly improved. The previous and subsequent MGD scores and Meiboscores were 12 to 10.50 and 2 to 1.50, respectively. MGD grade was examined in one study [22] with significant results, resulting in a previous and subsequent MGD grade of 3.6 ("Ropy" meibum) to 2.6 (Turbid and viscous oil appearance), respectively. LAMG was assessed in one study,[25] and it was greater after light therapy treatment. The previous and subsequent LAMG values were 10.9 to 16.7, respectively.

Risk of bias

Risk of bias assessment was classified into three evidence-level groups: studies with fewer than seven yeses (D'Souza et al.[24] and Solomos et al.[28]); studies with a value of seven yeses (Stonecipher et al.[22], Di Marino et al.[23] and Pérez-Silguero et al.[27]); studies with more than seven yeses (Marta et al.[25]).

DISCUSSION

IPL or LLLT single therapy has demonstrated to improve some signs and symptoms in dry eye patients. Park et al.[21] reported a statistically significant improvement among the mean differences of score changes in CFS and ST after 6 LLLT treatment sessions for 3 weeks. However, they reported nonsignificant improvement in OSDI, NIBUT and meibomian gland function. Regarding IPL single therapy, meta-analyses concluded that IPL therapy alone significantly improves NIBUT with controversial results on symptoms in dry eye patients.[2,32–34] This systematic review aimed to report the effects in symptoms and signs achieved with IPL combined with LLLT as a treatment for DED; positive results were shown in OSDI, tear film stability and meibomian gland function.

DED symptoms

Although there are different questionnaires that assess dry eye symptoms, the OSDI questionnaire is the most widely used for DED studies.[35] All studies included in this systematic review assessed dry eye symptoms with the OSDI questionnaire, and reported a significantly lower OSDI score after IPL combined with LLLT. Marta et al.[25] achieved the lowest OSDI score at the end of follow-up, performing three sessions

of IPL combined with LLLT in comparison to the other studies that performed 4 sessions [23,27,28] or a single session.[22,24] Di Marino et al.[23] only achieved a 12-point reduction in the OSDI score. This may be because the study population was patients with MDEs due to SSDE combined with MGD, while in the other studies, the study populations were patients with EDEs due to MGD. Some studies have reported that patients with SSDE have more severe MGD, leading to greater ocular surface changes and symptoms.[36,37]

The improvement in dry eye symptoms may be explained by the effect of IPL and LLLT on the meibomian glands. Energy produced by IPL causes thrombosis of the abnormal blood vessels and necrosis of the Demodex located in the eyelid and eyelashes, respectively.[7,15,16] Therefore, the concentration of inflammatory and microbial mediators that alter the meibomian glands is reduced, thus improving their function.[17] Moreover, IPL increases eyelid temperature, allowing the meibum to become more fluid [38,39]. This process is enhanced by the addition of LLLT, which is suggested to repair compromised cells, improve cell function, and increase meibomian gland heat by the production of ATP, leading to better meibum flow.[20,21] All this improves the lipid layer of the tear film, which increases the quality and integrity of the tear film, resulting in reduced dry eye symptoms.

Ocular surface in DED

Tear film stability, tear film volume, tear film composition and damage to ocular surface are tests recommended by TFOS DEWS II for the diagnosis of DED.[35] All included studies evaluated tear film stability. Stonecipher et al.[22], Di Marino et al.[23], D'Souza et al. and Solomos et al.[28] evaluated tear film stability with an invasive technique (BUT), while Marta et al.[25] and Pérez-Silguero et al.[27] performed a noninvasive technique (NIBUT). Marta et al.[25] was the only study that did not find a significant improvement in tear film stability. This may be because most of the study population had a pretreatment NIBUT of 10.2 s, while the other studies had a pretreatment NIBUT of 5.2 s or less. In addition, the DED diagnostic test battery created by the TFOS DEWS II suggests that a NIBUT below 10 s is a positive finding for DED.[35] Improvements in tear film stability in the other studies are due to an increase in tear film quality as a result of better meibomian gland function.

Tear film volume was assessed by TMH and ST. Marta et al.[25] and Pérez-Silguero et al.[27] measured THM with an IDRA Ocular Surface Analyser (SBM Sistemi, Torino, Italy) and Keratograph® 5 M (OCULUS Optikgeräte GmbH, Wetzlar, Germany), respectively. Both studies reported nonsignificant results in THM. Di Marino et al.,[23] D'Souza et al.,[24] Marta et al.[25] and Solomos et al.[28] measured ST, and only 1 study

reported significant results.[25] Tear volume, TMH and ST are related to lagrimal gland. These variables remained unchanged because IPL combined with LLLT aims to improves the lipid component of the tear due to the activation of the meibomian glands. Marta et al.[25] suggest that lacrimal gland secretion may be improved due to LLLT. However, Park et al.[21] reported controversial results in a RCT with LLLT therapy alone. Therefore, more studies are needed to justify the beneficial effects of the single or combined light therapy treatment on the lacrimal gland.

Tear film composition and damage to the ocular surface was determined by OSM and CFS, respectively. Tear hyperosmolarity is the main driver of DED.[35,37,40,41] Marta et al.[25] and Pérez-Silguero et al.[27] measured OSM with the TearLab Osmolarity System (TearLab, San Diego, CA, USA). Pérez-Silguero et al.[27] reported a significantly lower OSM after IPL combined with LLLT. Evaporation of the tear film is necessary to promote tear hyperosmolarity.[37] Therefore, improving the functionality of the meibomian glands with IPL combined with LLLT leads to an increase in tear film quality; thus, tear film evaporation is reduced, and tear osmolarity returns to normal values. However, Marta et al.[25] did not report a significant improvement in OSM. Some studies have suggested that current OSM measurement techniques are highly variable in DED patients.[42,43] For example, measuring tear OSM when tear film evaporates due to prolonged interblink periods may result in elevated tear OSM measurements, which may explain the results in this study.[44] Regarding damage to the ocular surface, Solomos et al.[28] reported that the degree of CFS, evaluated by the Oxford grading scale, was the same after light therapy treatment. However, Marta et al.[25] found a significant improvement in CFS, expressed as a percentage, but they did not grade CFS using a validated scale. Therefore, they could not effectively determine whether the degree of CFS decreased or remained unchanged. A better quality and integrity of tear film due to an improvement in meibomian gland function, which is achieved by IPL combined with LLLT, is the reason CFS is reduced.

Studies suggest that environmental factors such as low humidity and high temperature influence on CFS and OSM.[45–48] Moreover, Li et al.[49] reported that OSM may also vary over the course of 8 daytime hours. Marta et al.[25] and Solomos et al.[28] have not reported whether their measurements were performed at the same time of day and under the same environmental conditions, which may explain their results. In addition, it is important to consider that dry eye is a multifactorial and complex disease, which could explain the variability of all these results after IPL combined with LLLT.

Meibomian gland in DED

The International Workshop on Meibomian gland dysfunction recommends the following tests for the diagnosis of MGD: LLT, morphological lid features, quality and quantity of meibum and meibography.[50]

Marta et al.[25] measured LLT using the IDRA Ocular Surface Analyser (SBM Sistemi, Torino, Italy), Solomos et al.[28] evaluated morphologic lid features with the MGD score, Stonecipher et al.[22] assessed meibum quality and quantity with an MGD grade, and Solomos et al.[28] and Marta et al.[25] evaluated meibography with meiboscore and LAMG, respectively. All these studies reported significant results in LLT, MGD score, MGD grade and meiboscore after IPL combined with LLLT due to a better function of meibomian glands. However, Marta et al.[25] reported an increase in LAMG at the end of follow-up. The meibomian glands tend to alter over time, and there is insufficient scientific evidence on the growth and regeneration of gland tissue after IPL. In addition, Marta et al.[25] expressed LAMG as a percentage, and they did not grade meibography with a validation scale, as Solomos et al.[28] did with meiboscore; thus, they could not effectively determine whether the degree of meibography increased or remained unchanged.

Strengths and limitations

To the best of our knowledge, this is the first systematic review that describes IPL combined with LLLT outcomes in DED treatment. All studies included in this systematic review used the Eye-light device for DED treatment. Stonecipher et al.[22] used the Epi C-Plus device, which is the name given to the Eye-light device in the USA; thus, the methodology of all studies is remarkably similar. The main limitation of our review is that all studies included are series of cases, many of them having a retrospective design, but it is important to consider that IPL and LLLT are novel treatments for DED, and the scientific literature combining both treatments is extremely limited. Therefore, larger, well-designed, strictly blinded, multicentre RCTs with extensive follow-up are needed. Another limitation is that two from six studies included in this systematic review reported conflict of interest with Eye-light or Epi C-Plus device,[22,27] which represent a significant form of bias.

In conclusion, this systematic review demonstrated that IPL combined with LLLT may be indicated for DED owing to MGD. IPL combined with LLLT for the treatment of dry eye improves meibomian gland function, reducing symptoms and signs of dry eye, such as OSDI and tear film stability, respectively.

However, there is still not enough scientific evidence to suggest that this method of treatment is able to improve TMH, OSM, ST and CFS.

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FIGURE LEGENDS

FIG. 1. PRISMA flow chart diagram.

SUPPLEMENTAL DIGITAL CONTENT LEGEND

Supplemental Digital Content 1. Quality assessment of the articles.

The quality of the articles included in this systematic review was assessed through the following questions: (Q1): Was the study question clearly stated?; (Q2): Were all the patient results taken into account?; (Q3): Was the follow-up complete?; (Q4): Were the same conditions used in light therapy?; (Q5): Was the intervention clearly described?; (Q6): Was the length of follow-up adequate? (Q7): Were the statistical methods well-described? (Q8): Were the results well-described?

Table 2

Table 2. Study characteristics

Author (date)	Design	Follow-up (months)	Patients	Eyes	Age	Sex (M/F)	Type of DED	Light therapy device	Sessions	Time intervals (weeks)	IPL (E/FT)	LLLT (E/FT)	Conflict of interest
Stonecipher et al, 2019[22]	SC, RT, MT	3	230	460	65.5	60/170	EDE	Epi C-PLUS	NR	NR	10-16/600	110/633	Yes
Di Marino et al, 2021[23]	SC, RT, MN	3	20	40	57.7	2/18	ADDE EDE	Eye-Light	4	1	10-16/600	110/633	No
D'Souza et al, 2021[24]	SC, P, MN	6	47	94	NR	NR	EDE	Eye-Light	1	0	10-13/600	110/633	No
Marta et al, 2021[25]	SC, P, MN	6	31	62	66.9	12/19	EDE	Eye-Light	3	1	10-16/600	110/633	No
Pérez-Silguero et al, 2021[27]	SC, RT, MN	15	156	312	54.0	32/124	EDE	Eye-Light	4	1, 3, 8	10-16/600	110/633	Yes
Solomos et al, 2021[28]	SC, RT, MN	0.2	11	22	52.6	5/6	EDE	Eye-Light	4	1	10-16/600	110/633	No

ADDE, Aqueous-deficient dry eye; EDE, Evaporative dry eye; E, Energy (Expressed in j/cm$^{2)}$; FT, Filter (Expressed in nm); IPL, Intense pulse light; LLLT, Low-level light therapy; M/F, Male/Female; MN, Monocentric; MT, Multicenter; NR, Not reported; P, Prospective; RT, Retrospective; SC, Serie of Cases.

Table 3

Table 3. Evaluation of the clinical outcomes before and after IPL combined with LLLT on DED

Previous													
Author (date)	**OSDI**[a]	**NIBUT**	**BUT**	**TMH**	**OSM**	**ST**	**CFS**	**LLT**	**MGD Score**[d]	**MGD Grade**[e]	**Meiboscore**[f]	**LAMG**[b]	**Favor / Against**
Stonecipher et al, 2019[22]	42.2	NR	4.4	NR	NR	NR	NR	NR	NR	3.6	NR	NR	Favor
Di Marino et al, 2021[23]	50.5	NR	3.5	NR	NR	8.6	NR	NR	NR	NR	NR	NR	Favor
D'Souza et al, 2021[24]	39.1	NR	5.2	NR	NR	17.6	NR	NR	NR	NR	NR	NR	Favor
Marta et al, 2021[25]	45.0	10.2	NR	0.3	298.1	9.6	51.6[b]	47.4	NR	NR	NR	10.9	Favor
Pérez-Silguero et al, 2021[27]	58.3	4.3	NR	0.1	319.2	NR	NR	NR	NR	NR	NR	NR	Favor
Solomos et al, 2021[28]	33.7	NR	4.5	NR	NR	12.0	1[c]	NR	12.0	NR	2.0	NR	Favor
Posterior													
Author (date)	**OSDI**[a]	**NIBUT**	**BUT**	**TMH**	**OSM**	**ST**	**CFS**	**LLT**	**MGD Score**[d]	**MGD Grade**[e]	**Meiboscore**[f]	**LAMG**[b]	**Favor / Against**
Stonecipher et al, 2019[22]	24.2	NR	8.00	NR	NR	NR	NR	NR	NR	2.6	NR	NR	Favor
Di Marino et al, 2021[23]	38.3	NR	5.30	NR	NR	10.2	NR	NR	NR	NR	NR	NR	Favor
D'Souza et al, 2021[24]	24.4	NR	7.4	NR	NR	17.6	NR	NR	NR	NR	NR	NR	Favor
Marta et al, 2021[25]	8.2	9.9	NR	0.3	315.5	11.4	45.2[b]	73.9	NR	NR	NR	16.7	Favor
Pérez-Silguero et al, 2021[27]	28.2	7.3	NR	0.2	304.3	NR	NR	NR	NR	NR	NR	NR	Favor
Solomos et al, 2021[28]	19.2	NR	6.5	NR	NR	12.0	1[c]	NR	10.5	NR	1.5	NR	Favor

BUT, Break-Up Time (Expressed in seconds); CFS, Corneal Fluorescein Staining; DED, Dry Eye Disease; IPL, Intense Pulse Light; LAMG, Loss Area of Meibomian Gland (Expressed in percentage); LLLT, Low-Level Light Therapy; LLT, Lipid Layer thickness (Expressed in nm); MGD, Meibomian Gland Dysfunction; NIBUT, Non-Invasive Break-Up Time (Expressed in seconds); NR, Not reported; OSDI, Ocular Surface Disease Index; OSM, Osmolarity (Expressed in mOsm/L); ST, Schirmer's Test (Expressed in mm); TMH, Tear Meniscus Height (Expressed in mm).

[a]Values to 0 to 100 [b]Expressed in percentage; [c]Oxford grading scale; [d]Values to 0 to 15;[e]Values to 0 to 4; [f]Values to 0 to 6.

Figure 1