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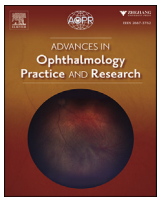

Full Length Article

Therapeutic effectiveness of different machines in intense pulsed light treatment of meibomian gland dysfunction

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ABSTRACT

Purpose: This study aimed to determine the therapeutic effectiveness of different machines in intense pulsed light (IPL) treatment of meibomian gland dysfunction (MGD).
Methods: 213 subjects diagnosed with MGD underwent three sessions of IPL treatment in a control (M22) treatment group or experimental (OPL-I) treatment group and were followed up three to four weeks after each session. Tear breakup time (TBUT), meibomian gland secretion scores (MGSS), meibomian gland meibum scores (MGMS), corneal fluorescein staining (CFS) scores, and the Standard Patient Evaluation of Eye Dryness (SPEED) was used to assess eye dryness signs and symptoms at baseline and follow-up visits.
Results: Two machines had the same working principles except that experimental (OPL-I) group consist of a dual filter system. Both groups showed significant improvements ($P < 0.0001$) in TBUT, MGSS, MGMS, CFS scores and SPEED scores. Non-inferiority analysis showed no statistically significant differences in any result between the two groups. Various defects appeared on the filter with the extension of usage time. Spectrophotometry showed that light intensity decreased to 93.5% ± 0.46% past the first filter.
Conclusions: IPL treatment completed with different machines have the same effect on improving the symptoms and signs of MGD. The dual filter system in the IPL machine reduces light intensity by approximately 6.5% without affecting its therapeutic effect. It is a feasible measure to ensure double safety and has the significance of popularization not only for MGD but also in other IPL treatment scenarios.

1. Introduction

Dry eye disease affects approximately 350 million individuals globally, with an estimated prevalence of 5%–50%, depending on the geographic region.[1] Meibomian gland dysfunction (MGD) is the leading cause of evaporative dry eye disease.[2,3] Various treatment options exist for MGD, including the application of a warm compress, lid hygiene practices, dietary supplementation with omega-3 fatty acids, automated thermal pulsation, lipid-containing eye drops, topical cyclosporine or azithromycin, and oral doxycycline.[4–8] Broadly, these treatments aim to restore the stability of the tear film by improving the lipid layer thickness or quality. However, many of them are supportive therapies that do not target the pathogenesis of MGD and relieve symptoms only temporarily.

IPL therapy is widely used to treat dermatological conditions[9] and is introduced for treating MGD since 2005.[10] Subsequent studies confirmed that IPL therapy can improve dry eye symptoms by improving meibomian gland function.[11,12] This led to rapid clinical uptake, and IPL treatment for MGD is now routinely performed as an in-office, multi-visit course of clinical care in more than 50 countries.[13] However, the improvement effect of IPL varies among different reports and the comparative study of effects between different IPL machines has not been reported.

IPL uses a high-output flash lamp to produce broad-wavelength, noncoherent light. Specific regions of the eyelids are exposed to brief flashes of light through a couplant gel layer to induce thrombosis of the telangiectatic blood vessels.[12] The light produced by the flash lamp is in the range of 300–1200 nm, which partly corresponds to ultraviolet (UV) light. A 590 nm filter is used during IPL therapy to filter out light below

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this wavelength and ensure that the light reaches deep into the capillary layer to guarantee safety. Nevertheless, some patients suffer damage to the periocular skin, such as depigmentation, swelling, or redness, which is slowly reversed without sequelae.[13]

Since IPL is a supportive and repeated treatment—patients usually need three or more sessions to achieve a satisfactory therapeutic effect—safety is the most important consideration. Light below a 420 nm wavelength belong to UV, which causes skin damage and aging, especially in the eyelids. Therefore, the presence of UV light is absolutely intolerable during IPL treatment. A filter that effectively filters out harmful light is the only guarantee of safety. However, there are no quality inspections or alarm systems for IPL machine filters. Filter defects can be identified only by visual observation, with or without a magnifying glass. Operators do not observe the filter before each operation and cannot detect small defects that are visible only through a magnifying glass. This poses a major safety hazard and a more secure filter system is of great significance to ensure the absolute avoidance of UV light during IPL treatment.

Based on above issues, we conducted a randomized controlled trial to investigate the therapeutic effectiveness of different IPL machines in MGD treatment. The experimental machine was equipped with a dual filter system to investigate its feasibility and necessity in IPL treatment.

2. Materials and methods

2.1. Trial design

This was a multicenter, two-arm parallel-group randomized active-controlled trial with a 1:1 allocation ratio conducted at the above-mentioned hospitals from November 2020 to August 2021. The trial aimed to assess therapeutic effectiveness of the study treatment arm (OPL-I with the dual filter system; Miracle Laser systems, Wuhan, China) to the control treatment arm (M22 with a single filter; Lumenis, Yokneam, Israel). Each MGD patient underwent three treatment sessions at three-week intervals and three follow-up examinations over the course of treatment. Apart from IPL treatment, all patients used a warming compress once a day and 0.3% hyaluronic acid eye drops (Hialid; Santen, Osaka, Japan) four times a day during the study without any other topical medication, including the follow-up period. Warming compress was achieved by steam warming eye mask with each session lasting 15 min.

2.2. Participants

The patient inclusion criteria were as follows: an age of 18–75 years, Fitzpatrick skin type I–IV according to sun sensitivity and skin appearance,[14] a Standard Patient Evaluation of Eye Dryness (SPEED) score of $\geq$6, tear breakup time (TBUT) of $\leq$10 s in the studied eye, corneal fluorescein staining (CFS) score of $\geq$1 (it is not necessary to consider this criterion if the TBUT is $\leq$ 5 s), and meibomian gland secretion score (MGSS) of $\geq$6 in the studied eye. The MGSS evaluates the obstruction of meibum along the lower eyelid.[15] Three positions along the lower eyelid were detected using a meibomian gland evaluator. A score of 0 indicated secretion by all five glands, a score of 1 indicated secretion by three to four glands, a score of 2 indicated secretion by one or two glands, and a score of 3 indicated no secretion by any glands.

2.3. Clinical assessment

The safety of IPL treatment was evaluated by best-corrected visual acuity and intraocular pressure measurements and slit-lamp examinations at baseline and at the final visit. To evaluate treatment efficacy, the following parameters were measured at baseline and at each follow-up visit: TBUT, CFS scores, and meibomian gland function according to MGSSs and meibomian gland meibum scores (MGMSs). The MGMS evaluates the quality of meibum along the lower eyelid, with a score of 0 indicating clear liquid meibum, a score of 1 indicating cloudy liquid meibum, a score of 2 indicating cloudy granular meibum, and a score of 3 indicating toothpaste-like solid meibum). Symptoms were assessed using the validated SPEED questionnaire.

2.4. IPL treatment

Before the first IPL session, the IPL machines were adjusted to the appropriate setting according to each patient's Fitzpatrick skin type (range of 11–14 J/cm^2).[16] Immediately after treatment, meibomian gland compression was performed on both the upper and lower eyelids of each eye with a Meibomian Gland Compressor.

2.5. Statistical analysis

We chose non-inferiority analysis to evaluate the therapeutic effectiveness of two IPL machines. The difference in TBUT in the studied eye between the baseline and the third visit (three weeks after the third IPL session) was used as the main evaluation index and the basis for sample size calculation. The TBUT non-inferiority margin for the dual filter was defined as -0.9 ± 2.1 s, according to a previous clinical trial.[17] The calculation formula was as follows:

$$n_T = n_c = \frac{2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)}{\left(|D| - \triangle\right)^2}$$

where σ is the expected standard deviation of the control group, $|D|$ is an absolute value indicating the difference between the means of the two arms, and Δ is the non-inferiority margin. The TBUT of each group was calculated at an α level of 0.025 (unilateral test) and a β level of 0.2. In principle, the non-inferiority margin should not exceed half of the control effect minus the placebo effect. When the margin is difficult to determine, 1/2 of the standard deviation can be used.[18] All statistical tests were two-sided, and P values of $<$0.05 were considered statistically significant. The statistical analysis was performed using Prism 9.4.1 software.

2.6. Filter observation and spectral detection

The filter was examined under a dissecting microscope, and representative images were taken. The spectrum produced by the flash lamp was detected using a spectrophotometer.

2.7. Ethics statement

This study was approved by the Institutional Review Boards of the Second Affiliated Hospital of Zhejiang University (Approval ID: 2019LSXD No.359), Institutional Review Boards of Wuhan Aier Eye Hospital (Approval ID: 20201RBQX15), Institutional Review Boards of Hankou Aier Eye Hospital (Approval ID: HKAIER2020IRB-002-03) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient before enrollment.

3. Results

3.1. Difference analysis between two IPL machines

The similarities and differences between two IPL machines are shown in Table 1. The main difference of the two machines was their filter system. Experimental group consist of a dual filter system by adding a safety filter of 420 nm before selective filter of 590 nm.

3.2. Baseline values

Treatment and follow-up protocol for the two groups are shown in Fig. 1. The participants' baseline characteristics are shown in Table 2. There was no statistically significant difference in terms of gender distribution, age distribution, Fitzpatrick skin types distribution, dry eye

Table 1
Difference analysis between two IPL machines.

		Control group (M22)	Experimental group (OPL-I)
Similarities	Lighting source	Water-cooled straight tube xenon lamp	
	Lighting principle	Pulsed light	
	Skin cooling system	Sapphire contact conduction cooling	
	Number of sub pulse	3	
	Light energy for MGD	11–14 J/CM^2	
Differences	Filter system for MGD	Single filter (590 nm)	Dual filter (420 nm and 590 nm)
	Spot size for MGD	15mm^2*35 mm^2	8mm^2*34 mm^2

grades distribution and MGD grades distribution between the two arms. Similarly, there were no statistically significant differences in baseline MGSS ($P = 0.70$), MGMS ($P = 0.73$), TBUT ($P = 0.98$), CFS scores ($P = 0.35$), or SPEED scores ($P = 0.50$) between the two groups (see Table 3).

3.3. Changes in sign endpoints and symptom endpoint after IPL treatment in the two groups

The changes in the primary signs and symptom are shown in Fig. 2. In both arms, the MGSSs decreased, indicating increased meibomian gland patency, and the effect gradually strengthened as the sessions progressed (Fig. 2A–B). The MGMSs also gradually decreased in both arms, indicating improved meibum quality (Fig. 2C–D). The TBUT gradually increased in both arms as the sessions progressed (Fig. 2E–F). The CFS scores and SPEED scores also gradually decreased in both arms (Fig. 2G–J). These results indicated a significant improvement in MGD signs and symptom in both arms, confirming the effectiveness of IPL treatment.

3.4. Non-inferiority analysis

The non-inferiority analysis showed that the 95% confidence intervals of all evaluation endpoints were higher than the margins, indicating that the treatment with experimental group was as effective as that with the control group (Table 2).

3.5. Filter defects and dual filter system design

The spectrophotometry analysis showed that the light emitted from the high-output flash xenon lamp before filtering was in the range of 300–1200 nm, which partly corresponds to harmful UV light, mainly UVA-1 (340–420 nm) (Fig. 3A). An investigation of the 590 nm filter of the M22 machine, which had been used for approximately three years, showed multiple defects all over the filter that could affect its function (Fig. 3B–C) and may lead to skin pigmentation and aging (Fig. 3D). The design of dual filter system is shown in Fig. 3E. The spectrophotometry analysis of light intensity showed that the 420 nm filter filtered out nearly 100% of the wavelengths below 425 nm and attenuated the wavelengths above 425 nm to approximately 93.5% (Fig. 3F–G).

3.6. Adverse events

There were no changes in intra-ocular pressure, best-corrected visual acuity, or anterior segment inflammation in either group (not shown). During this clinical trial, dual filter group reported a total of 21 adverse events, while the control group reported 30 adverse events. Two device-related adverse events (visual fatigue, eyelid swelling, conjunctivitis, skin redness) occurred in the dual filter group and the control group respectively. All adverse events were relieved or disappeared at the end

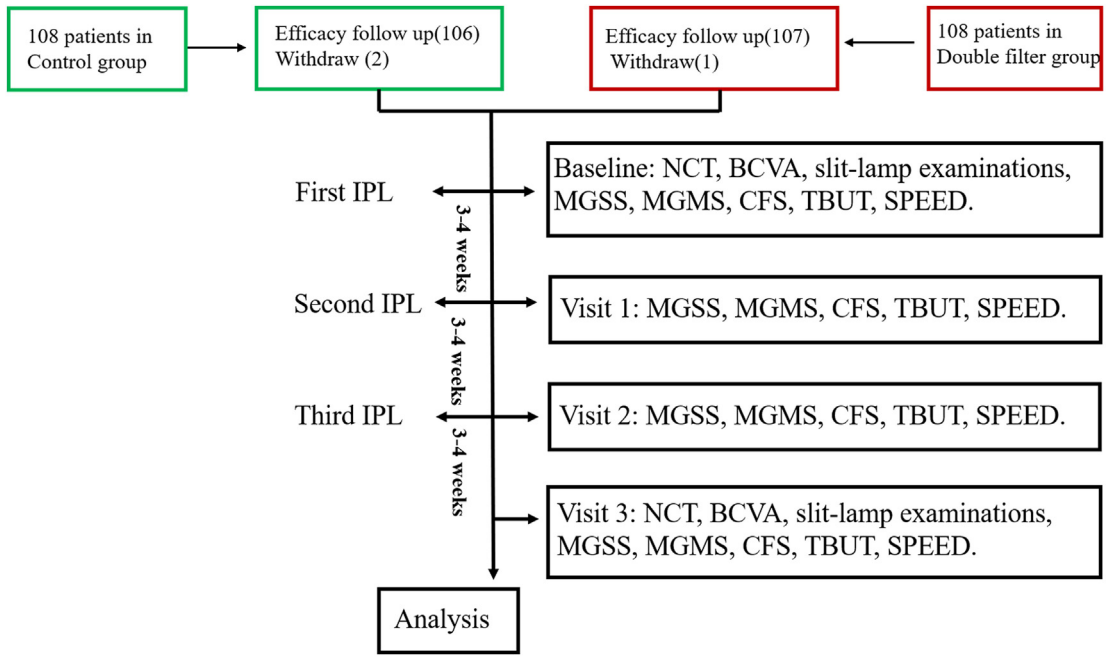

Fig. 1. Trail design.
Schematic diagram of the randomized controlled trial design.
NCT, Non-contact tonometer; BCVA, Best corrected visual acuity; TBUT, Tear breakup time; MGSS, Meibomian gland secretion scores; MGMS, Meibomian gland meibum scores; CFS, Corneal fluorescein staining; SPEED, Standard Patient Evaluation of Eye Dryness.

Table 2
Baseline characteristics between the control and experimental groups.

	Control group (M22)	Dual filter group	*P*-value
Demographics			
N (subjects)	107	108	
Age [yr, (SD)]	38.98 (12.537)	40.81 (13.410)	0.3038
Sex			0.2798
Male	32	25	
Female	76	83	
Skin type			0.5899
TypeII	17	23	
TypeIII	81	77	
TypeIV	9	8	
Dry eye sign endpoints			
MGSS [mean, (SD)]	6.74 (1.14)	6.80 (1.39)	0.6982
MGLS [mean, (SD)]	1.35 (0.67)	1.32 (0.67)	0.7259
TBUT (s)[mean, (SD)]	3.37 (1.37)	3.36 (1.29)	0.985
CFS score [mean, (SD)]	0.71 (0.88)	0.59 (0.96)	0.349
Dry eye symptom endpoints			
SPEED socre [mean, (SD)]	6.91 (1.12)	7 (0.92)	0.5039
Distribution of dry eye grades			
Mild	91	80	0.142
Moderate	13	24	
Severe	4	4	
Distribution of MGD grades			
Mild	6	5	0.901
Moderate	68	69	
Severe	34	34	

[1]*t*-test p-value,[2]Chi-Square *P*-value.

Table 3
Non-inferiority analysis between two groups.

	Difference between two groups	Non-inferiority Margin	Non-inferiority
Main evaluation endpoint			
TBUT(s) [△mean, (CI95)]	−0.19 (−0.80,0.41)	−0.9	Yes
Secondary evaluation endpoint			
MGSS [△mean, (CI95)]	−0.11 (−0.67,0.44)	−0.9925	Yes
MGLS [△mean, (CI95)]	−0.06 (−0.26,0.13)	−0.3425	Yes
CFS score [△mean, (CI95)]	−0.18 (−0.43,0.06)	−0.885	Yes
SPEED score [△mean, (CI95)]	−0.16 (−0.66,0.34)	−0.98	Yes

of the clinical trial. The degree of adverse events was mild or moderate, and no serious adverse events occurred.

4. Discussion

IPL treatment for MGD has been proven effective in multiple studies, but most studies focused on patients with specific MGD or eye dryness grades with a relatively small enrolled sample sizes and the improvement effect of IPL varies among different reports.[19] The effectiveness differences between different IPL machines should be clarified, and research involving larger and broader populations is also needed. Our trial compared the therapeutic effectiveness of two different IPL machines and enrolled the largest MGD population to date (206 patients; 203 patients with completed follow-up) with all degrees of eye dryness grading and MGD grading. Our results show that IPL treatment can gradually improve meibomian gland function and dry eye signs and symptoms. The non-inferiority analysis show that there is no significant difference of effectiveness between different IPL machines. This study further confirms the therapeutic effect of IPL.

Our study suggest that accumulated IPL machine filter defects may pose a latent danger to the eyelids. We confirmed that the high-output flash xenon lamp emitted light in the range of 300–1200 nm, which partly corresponds to UV light, mainly UVA-1 (340–420 nm). UVA-1 is a clear promotor of skin ageing by induction of matrix degrading metalloproteases and of skin cancer by induction of photochemical DNA mutations such as cyclopyrimidine dimers, which can accumulate with repeated exposure.[20,21] As one of the thinnest skin, the eyelid is particularly vulnerable to UV light, resulting in pigment deposition, wrinkles, and aging, which directly affect appearance. Since IPL is a supportive treatment, complete safety is the most important concern. The filter is the only device that can prevent UV leakage and it is difficult for the operator to check the filter under magnifying glass before each use. Furthermore, if the filter is discarded once a slight defect is detected, this will create a financial burden.

Dual filter systems are widely and effectively used in environmental governance, such as sewage treatment and odor filtration, to ensure safety.[22] Such systems are also widely used in medicine. Dual filter systems are used to provide embolic protection to reduce secondary infarction in arteries such as aortic, carotid and vertebral arteries.[23,24] They are also used in autologous fat grafting surgery to ensure the purity of the implanted fat.[25] Thus, dual filter systems offer patients undeniable benefits and are simple, effective, and economical.

Our study evaluates the feasibility and necessity of dual filter system for an IPL machine. We found that although the dual filter system resulted in a light intensity reduction to approximately 93.5%, the effectiveness of the treatment with the dual filter was similar to that of the treatment with the single filter. Thus, despite the decrease in light intensity, the dual filter system offers comparable effectiveness and greater safety, which has the significance of popularization.

Besides MGD, other scenarios of IPL treatment for dermatological conditions and especially for cosmetic dermatology, such as removal of hypertrichosis and pigmented lesions and improvement of skin condition, also need to be considered. We should make every effort to reduce direct skin exposure to UV since its impact can be conceal and long-term.

Certain limitations of this study should be acknowledged. It was impossible to artificially create the same multiple filter defects during spectrophotometry analysis. Therefore, we could not determine the intensity of UV light leaking from the defective filter. We believe that even if UV intensity could be detected, it would be very low, given that most defects are so small that they can be observed only under a microscope. However, because there is only a couplant gel layer of approximately 1 mm between the light and the skin during IPL treatment, as UV light is concentrated in the filter defect areas, it may reach a harmful intensity locally and cause skin damage. Another limitation is that the follow-up period lasted only three months, which was not sufficient to evaluate the long-term effects of IPL treatment with the dual filter system. Therefore, studies with longer follow-up periods are required.

In conclusion, this study shows that different IPL machines have the similar therapeutic effectiveness during MGD treatment. Dual filter system for the IPL machine is a simple, easily operable, and economical measure to guarantee complete safety and has the significance of popularization in the IPL therapy for MGD. Further researches are needed to verify the equivalence of the dual filter system in other IPL treatment scenarios such as cosmetic dermatology.

Study approval

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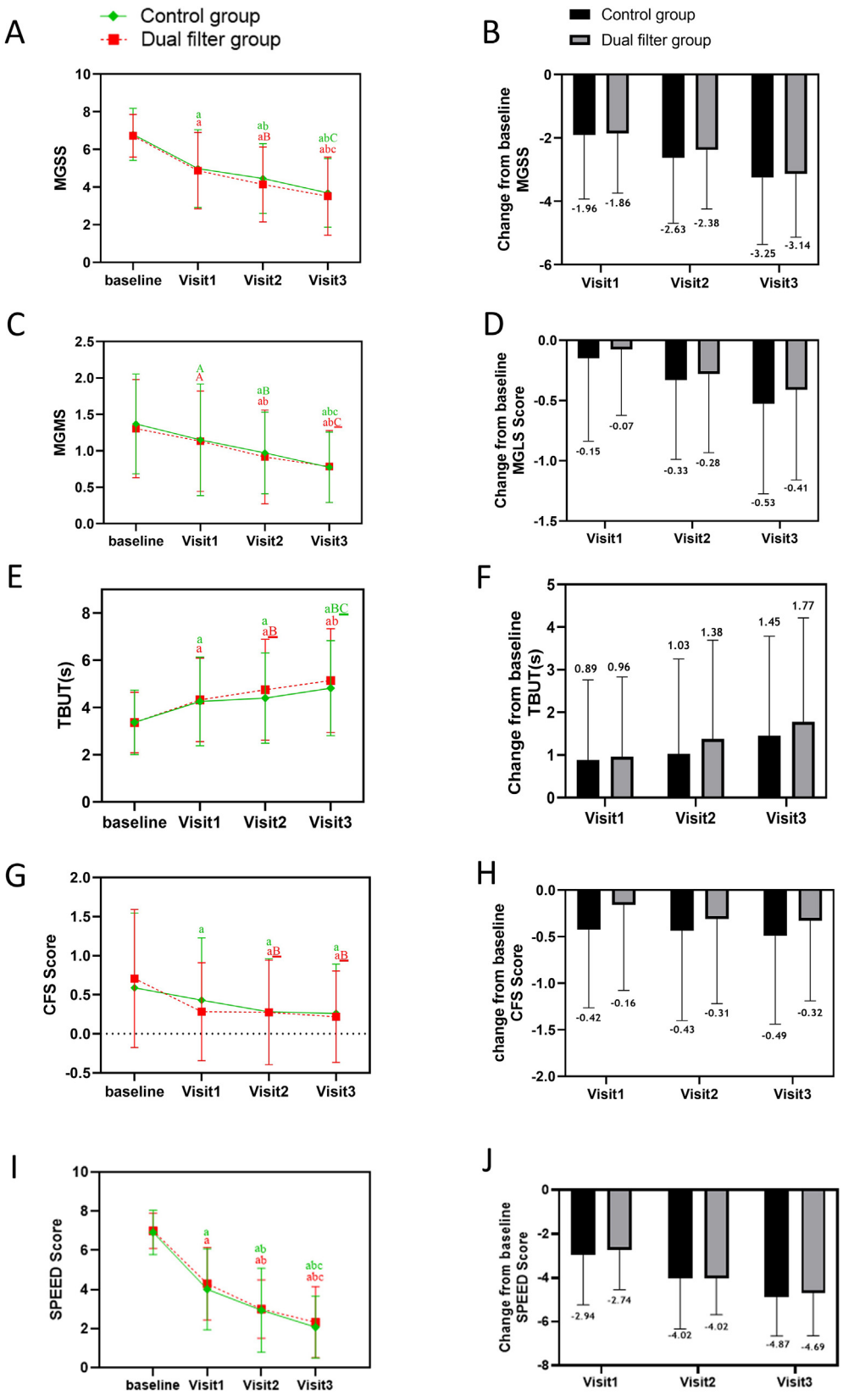

Fig. 2. Improvement of signs and symptom after IPL. (A). MGSS at baseline and at the three follow-up visits. (B). Changes in MGSS from the baseline to the third visit. (C and D). MGMS and it's changes at baseline and the follow-up visits. (E and F). TBUT and it's changes at baseline and the follow-up visits. (G and H). CFS and it's changes at baseline and the follow-up visits. (I and J). SPEED scores and it's changes at baseline and the follow-up visits. a: $P < 0.001$ compared to baseline; A: $P < 0.01$ compared to baseline; b: $P < 0.001$ compared to visit 1; B: $P < 0.01$ compared to visit 1; B: $P < 0.05$ compared to visit 1; c: $P < 0.001$ compared to visit 2; C: $P < 0.01$ compared to visit 2; C: $P < 0.05$ compared to visit 2.

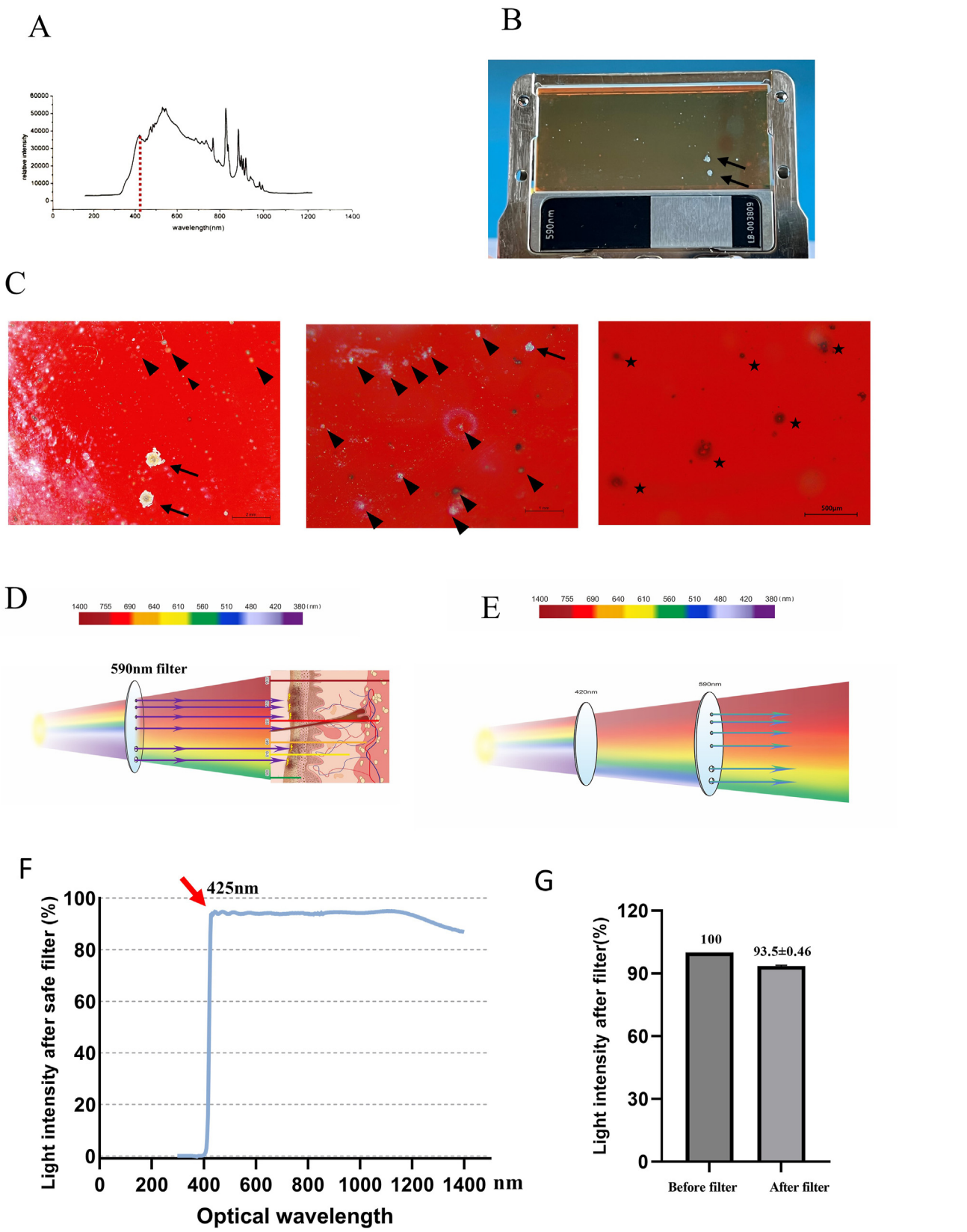

Fig. 3. Filter defects and dual filter system design. (A). Spectrum of the pulse xenon lamp analyzed with a spectrophotometer. Wavelengths below 420 nm (red line) correspond to UV light. (B). Typical image of visible filter defects (black arrows). (C). Representative micrographs of filter defects, including filter coating loss (marked with the black arrow and triangle) and pre–coating loss (marked with the black pentagram). (D). Leaked UV light poses a latent danger to the eyelid. (E). Design of dual filter system. (F). The inflection point of the filtering wavelength of the filter is 425 nm (red arrows) (G). Reduction of light intensity.

adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient before enrollment.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: XMJ, ZWQ, QYZ, JHW; Data collection: ZWQ, YRZ, JLL, LL, YNH, HYW, CQ, XXC; Analysis and interpretation of results: ZWQ, YRZ, JLL; Drafting the manuscript: ZWQ; Reviewing and editing of the manuscript: XMJ. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

IPL, Intense pulsed light; MGD, Meibomian gland dysfunction; TBUT, Tear breakup time; MGSS, Meibomian gland secretion scores; MGMS, Meibomian gland meibum scores; CFS, Corneal fluorescein staining; SPEED, Standard Patient Evaluation of Eye Dryness; NCT, Non-contact tonometer; BCVA, Best corrected visual acuity; UV, Ultraviolet

References

1. Nelson JD, Craig JP, Akpek EK, et al. TFOS DEWS II introduction. *Ocul Surf*. 2017;15(3):269–275. https://doi.org/10.1016/j.jtos.2017.05.005.
2. Nelson JD, Shimazaki J, Benitez-del-Castillo JM, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. *Invest Ophthalmol Vis Sci*. 2011;52(4):1930–1937. https://doi.org/10.1167/iovs.10-6997b.
3. Tomlinson A, Bron AJ, Korb DR, et al. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. *Invest Ophthalmol Vis Sci*. 2011;52(4):2006–2049. https://doi.org/10.1167/iovs.10-6997f.
4. Qiao J, Yan X. Emerging treatment options for meibomian gland dysfunction. *Clin Ophthalmol*. 2013;7:1797–1803. https://doi.org/10.2147/OPTH.S33182.
5. Greiner JV. A single lipiflow thermal pulsation system treatment improves meibomian gland function and reduces dry eye symptoms for 9 months. *Curr Eye Res*. 2012;37(4):272–278. https://doi.org/10.3109/02713683.2011.631721.
6. Giannaccare G, Pellegrini M, Sebastiani S, et al. Efficacy of omega-3 fatty acid supplementation for treatment of dry eye disease: a meta-analysis of randomized clinical trials. *Cornea*. 2019;38(5):565–573. https://doi.org/10.1097/ICO.0000000000001884.
7. Thode AR, Latkany RA. Current and emerging therapeutic strategies for the treatment of meibomian gland dysfunction (mgd). *Drugs*. 2015;75(11):1177–1185. https://doi.org/10.1007/s40265-015-0432-8.
8. Vernhardsdottir RR, Magno MS, Hynnekleiv L, et al. Antibiotic treatment for dry eye disease related to meibomian gland dysfunction and blepharitis - a review. *Ocul Surf*. 2022;26:211–221. https://doi.org/10.1016/j.jtos.2022.08.010.
9. Gade A, Vasile GF, Rubenstein R. *Intense Pulsed Light (Ipl) Therapy*. 2022.
10. Toyos R, McGill W, Briscoe D. Intense pulsed light treatment for dry eye disease due to meibomian gland dysfunction; A 3-year retrospective study. *Photomed Laser Surg*. 2015;33(1):41–46. https://doi.org/10.1089/pho.2014.3819.
11. Toyos R, Buffa C, Youngerman S. Case report- Dry–eye symptoms improve with intense pulsed light treatment. *EyeWorld*. 2005;33:41–46.
12. Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. *Ocul Surf*. 2019;17(1):104–110. https://doi.org/10.1016/j.jtos.2018.11.004.
13. Cote S, Zhang AC, Ahmadzai V, et al. Intense pulsed light (ipl) therapy for the treatment of meibomian gland dysfunction. *Cochrane Db Syst Rev*. 2020;3(3):D13559. https://doi.org/10.1002/14651858.CD013559.
14. Fitzpatrick TB. The validity and practicality of sun-reactive skin types i through vi. *Arch Dermatol*. 1988;124(6):869–871. https://doi.org/10.1001/archderm.124.6.869.
15. Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. *Cornea*. 2008;27(10):1142–1147. https://doi.org/10.1097/ICO.0b013e3181814cff.
16. Giannaccare G, Taroni L, Senni C, Scorcia V. Intense pulsed light therapy in the treatment of meibomian gland dysfunction: current perspectives. *Clin Optom*. 2019;11:113–126. https://doi.org/10.2147/OPTO.S217639.
17. Yan X, Hong J, Jin X, et al. The efficacy of intense pulsed light combined with meibomian gland expression for the treatment of dry eye disease due to meibomian gland dysfunction: a multicenter, randomized controlled trial. *Eye Contact Lens*. 2021;47(1):45–53. https://doi.org/10.1097/ICL.0000000000000711.
18. Hahn S. Understanding noninferiority trials. *Korean J Pediatr*. 2012;55(11):403–407. https://doi.org/10.3345/kjp.2012.55.11.403.
19. Tashbayev B, Yazdani M, Arita R, Fineide F, Utheim TP. Intense pulsed light treatment in meibomian gland dysfunction: a concise review. *Ocul Surf*. 2020;18(4):583–594. https://doi.org/10.1016/j.jtos.2020.06.002.
20. Schneider LA, Raizner K, Wlaschek M, Brenneisen P, Gethoffer K, Scharffetter-Kochanek K. Uva-1 exposure in vivo leads to an il-6 surge within the skin. *Exp Dermatol*. 2017;26(9):830–832. https://doi.org/10.1111/exd.13286.
21. Tewari A, Grys K, Kollet J, Sarkany R, Young AR. Upregulation of mmp 12 and its activity by uva 1 in human skin: potential implications for photoaging. *J Invest Dermatol*. 2014;134(10):2598–2609. https://doi.org/10.1038/jid.2014.173.
22. Xu Z, Sui Q, Li A, et al. How to detect small microplastics (20-100 mum) in freshwater, municipal wastewaters and landfill leachates? A trial from sampling to identification. *Sci Total Environ*. 2020;733:139218. https://doi.org/10.1016/j.scitotenv.2020.139218.
23. Voss S, Ernst A, Erlebach M, et al. Effects of a dual-filter-based cerebral embolic protection device in transcatheter aortic valve replacement on cerebral oxygen saturation: a prospective pilot study. *J Card Surg*. 2021;36(4):1241–1248. https://doi.org/10.1111/jocs.15355.
24. Shah AS, Akhmerov A, Gupta N, Chakravarty T, Makkar RR, Azizzadeh A. Use of a dual-filter cerebral embolic protection device in thoracic endovascular aortic repair. *Ann Vasc Surg*. 2020;65:51–54. https://doi.org/10.1016/j.avsg.2020.01.077.
25. Assad M, Howell SM, Liu J, et al. The effect of lipoaspirate processing technique on complications in autologous fat grafting for breast reconstruction: a propensity score analysis study. *Aesthetic Surg J*. 2021;41(10):P1303–P1309. https://doi.org/10.1093/asj/sjab235.