Indirect Effects of Intense Pulsed Light in Treating Meibomian Gland Dysfunction— A Prospective, Randomized, Double-Masked Trial

Yu Cheng
Peking University First Hospital
Wenjing Song
Peking University First Hospital
Songlin Yang
Peking University First Hospital
Xiaoming Yan (yanxiaoming7908@163.com)
Peking University First Hospital

Research Article

Keywords: intense pulsed light, dry eye, meibomian gland dysfunction, photobiomodulation

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1421069/v1

Abstract

Purpose

This study was designed to explore the indirect effects of intense pulsed light (IPL) treatment for meibomian gland dysfunction (MGD).

Methods

This trial was registered in the Chinese Clinical Trial Registry (ChiCTR1800019160) on October 26th, 2018. Sixty participants with MGD were enrolled in a prospective randomized double-masked trial. Three IPL treatments were performed at distances of 3 mm (Group A) and 10 mm (Group B) from the lower eyelid margin at 3-week intervals. The meibomian gland yield secretion score (MGYSS) and tear film parameters were evaluated at baseline and at 3 weeks after each treatment. Symptomology and corneal nerves were assessed at baseline and at 3 weeks after the third treatment.

Results

MGYSS (of both upper and lower eyelids) and Standard Patient Evaluation of Eye Dryness (SPEED) scores improved in both groups after three IPL treatments (all $p < 0.05$), changes of both of which did not differ between the two groups. Tear film parameters and corneal subepithelial nerve density were maintained in both groups at levels equal to baseline levels.

Conclusion

IPL improves the function of meibomian glands and relieves the symptoms of related dry eye to the same degree at different distances of the IPL beam's proximity to the lower eyelid margin in the short term, which implies the probable existence of indirect effects of IPL.

Introduction

Intense pulsed light (IPL) has been proven effective for treating meibomian gland dysfunction (MGD) and relieving related dry eye disease [1–6]. Clinically, for patients who have tried other therapies without receiving satisfactory outcomes, IPL is a potential option. As a result, patients who choose IPL tend to be long sufferers of this disease, with moderate to severe MGD. In the aspect of treating area, almost all the articles have described it as up to the inferior boundary of the eye shields (i.e., protective eye pads). As we know, the length of meibomian glands in the lower eyelid is approximately 2 mm [7]. The inferior boundaries of eye shields are usually much more than 2 mm away from the lower lid margin. Thus, for meibomian glands in lower eyelids, IPL treatment is actually applied indirectly.

Furthermore, Dell et al. [8] reported improvement in the upper lid meibomian glands with IPL treatment applied only to the skin up to the inferior boundary of the eye shields. Similarly, Rodrigo et al. [9] researched the systematic effects of low-level laser therapy (LLLT) in a rat model. They produced three wounds on backs of the rats, following the midline from head to tail at 7 cm intervals. The laser beam was only applied to the wound closest to the head. Their results showed that the healing process had been stimulated in all three wound sites [9]. Combined with the indirect effects of IPL mentioned before, it is reasonable to speculate that the beam can be located farther from the eye to enhance the safety margin of this treatment while satisfactory outcomes are preserved.

Thus, in this study, we explored the indirect effects of IPL treatment in MGD patients by treating two groups with different distances from the lower eyelid margin and comparing outcomes between them. We did not perform meibomian gland expression (MGX) after each treatment as usual, as we were interested in observing the indirect effects of IPL, not to be mixed or covered by the effects of MGX.

Methods

This prospective, randomized, double-masked clinical trial followed the principles of the Declaration of Helsinki and was registered in the Chinese Clinical Trial Registry (ChiCTR1800019160). Approval from the Human Research and Ethics Committee of Peking University First Hospital was attained before enrollment began. All participants signed informed consent before any examinations or treatments were performed. The inclusion and exclusion criteria refer to our previous trial on IPL treatment. [10]

Subjects were randomly assigned to two treatment groups in which the IPL beam was applied at distances from the lower eyelid margin of 3 mm (Group A) and 10 mm (Group B). Randomization was performed by the IPL therapist using a random number table after subjects met the inclusion and exclusion criteria. The observer and subjects remained masked over the duration of the trial.

We used the M22 system (Lumenis, Tel Aviv, Israel) to perform IPL treatments at the forehead, bilateral temporal area, and at 3 or 10 mm (Group A or B, respectively) from the margins of the lower eyelids in the cheek area [11], with a 590nm filter used. The energy densities ranged from 12 to 15 J/cm2 according to the Fitzpatrick skin type and the subject's tolerance for pain, with 14–18 overlapping IPL treatment exposures (15 mm × 35 mm, each) in the treatment area. No treatment was applied on the upper eyelids. Eyes were protected by masks. The first IPL treatment was performed within 3 weeks after enrollment; the following two treatments were performed at 3-week intervals. Patients using artificial tears as part of their treatment were allowed to continue. The primary outcome was the meibomian gland yield secretion score (MGYSS). Other symptoms and signs were secondary outcomes.

MGYSS was measured with a meibomian gland evaluator (Tear Science Inc., Morrisville, North Carolina, USA). The procedure was performed following Lane's protocol [12]. Scores of 15 glands in each eyelid were summed to obtain a single MGYSS. The Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire was applied to evaluate the severity and frequency of dry eye symptoms. Tear break-up time (TBUT) was measured using moist fluorescein sodium strips (Jingming New Technological

Development Co, Ltd, Tianjin, China). The average TBUTs of three repeated measurements were recorded. Corneal fluorescein staining (CFS) was graded following the protocol Described in our previous work. [10] Central corneal subepithelial nerves (CCSN) were observed by in vivo laser confocal microscopy (IVCM) (Heidelberg Retina Tomograph II-Rostock Cornea Module: HRTII-RCM; Heidelberg Engineering GmbH, Dossenheim, Germany). Each image covers a 400 × 400 μm2 area. Image J software (National Institutes of Health, Bethesda, MD, USA) was used to trace the nerves and to calculate the whole length of CCSN in the designated area. Three representative images were selected for tracing and calculating each eye at each time point. The average of the three was recorded. MGYSS and TBUT were observed at each visit; the other parameters were assessed only at baseline and the last visit.

SPSS 22.0 for Windows software (SPSS Inc., Armonk, New York, USA) was used for the statistical analyses. We chose data from the right eye of each patient (60 eyes from 60 patients) for our analyses. According to a previous study [4], the standard deviation of MGYSS of the lower eyelids (l – MGYSS) at baseline was 3.3. As for the noninferiority threshold, we referred to our previous study that compared change of l-MGYSS between the IPL + MGX group and the warm compress + MGX group [10]. It was calculated to be 2.8, based on the change in value of the IPL + MGX group minus the change in value of the warm compress + MGX group after three treatments compared to baseline. This noninferiority threshold represented only the partial beneficial effects of IPL that exceeded the effects of using a warm compress, as opposed to an effect based solely on IPL. Therefore, with a smaller noninferiority threshold, we would expect to obtain a more conservative/larger sample size. The sample size was chosen to achieve a statistical power of 80% at a 5% significance level while considering 20% loss to follow-up. The sample size calculation indicated that an enrollment of 27 subjects in each group would meet the above-mentioned design. The sample size was finalized as 30 subjects for each group, 60 in total. Descriptive statistics of continuous variables were reported as the mean ± standard deviation. Data from the same group were compared at two time points using a paired t test. An independent sample t test or a Mann–Whitney U test was conducted to compare data between the two treatment groups at the same time point, as appropriate. The descriptive statistics of categorical variables were expressed as frequencies or proportions/percentages. Analyses of categorical statistics were performed using a chi-square test. For all tests, $p < 0.05$ was considered statistically significant. We performed intention-to-treat analyses. Missing values were handled by inputting the missing value using the last observation carried forward.

Results

Sixty subjects were enrolled in the study and randomly allocated to two treatment groups: 32 in Group A (3 mm) and 28 in Group B (10 mm). In Group A, two subjects withdrew before the first treatment and three subjects were lost to follow-ups. In Group B, one subject withdrew before treatment and two subjects were lost to follow-ups. Demographic features did not differ between two groups (all $p > 0.05$, Table 1).

The u-MYGSS (MGYSS of upper eyelids) l-MYGSS(MGYSS of lower eyelids) and T-MYGSS(total MGYSS of both upper and lower eyelids) did not differ between Group A and Group B at baseline. (Table 2) After three IPL treatments, both groups showed significant improvement in MGYSS compared to baseline. (P

values of u-MGYSS, l-MGYSS, T-MGYSS in Group A were 0.007, 0.003, 0.001, P values of u-MGYSS, l-MGYSS, T-MGYSS in Group B were all < 0.001). (Fig. 1) Furthermore, as Fig. 1 shows, effects on MGYSS had already shown after the second treatment. Change values and rates of u-MGYSS, l-MGYSS and T-MGYSS after three treatments compared to baseline did not significantly differ between Group A and Group B. (Table 3)

Scores of SPEED questionnaire did not differ between Group A and Group B at baseline. (Table 2) After three IPL treatments, both groups showed decline in scores (P values of both groups were < 0.001). (Fig. 2) Change values of SPEED scores after three treatments compared to baseline did not differ between the two groups. (Table 3)

TBUT did not differ between Group A and Group B at baseline. (Table 2) After three treatments, we observed subtle improvement in both groups. However, the improvement was not statistically- significant in either of them.

CFS did not differ between the two groups at baseline. (Table 2) After three treatments, both groups showed fine decreases in CFS (-0.54 ± 1.25 in Group A, -0.22 ± 1.70 in Group B), which were not statistically significant(Group A: p = 0.27, Group B: p = 1.00).

We considered the whole length of central corneal subepithelial nerves in a 400 × 400-μm area as a replacement for density. The density of central corneal subepithelial nerves did not differ between the two groups. (Table 2) After three IPL treatments, the densities of Group A and Group B showed no statistically significant change (Group A: p = 0.73, Group B: p = 0.64).

Discussion

This trial showed that two groups using IPL treatment of MGD alone, without MGX, and with different distances of the IPL beam with respect to the lower lid margin (3 and 10 mm) had similar outcomes regarding improved meibomian gland function in both upper and lower eyelids (evaluated by MGYSS) and relief of related dry eye symptoms (evaluated by SPEED questionnaire). The results answered the question that motivated us at first place. We may move the beam farther from the eye to guarantee a safer and equally helpful protocol. The results further corroborate indirect effects of IPL. To date, there has not been theory explaining the indirect effects of IPL. In other light therapy areas, there are studies reporting similar stories on indirect effects and placing photobiomodulation (PBM) as an important explanation. We speculate that PBM may also be the mechanism of IPL indirect effects.

PBMs are produced by coherent or noncoherent light sources or both within the visible and near-infrared (NIR) spectra. Its effects start from the chromophore inside cells absorbing the energy. A series of photophysical and photochemical reactions are elicited at the molecular and cellular levels. Eventually, various effects on tissues, such as changes in cell proliferation and differentiation, RNA and protein synthesis, oxidative stress and inflammatory processes are produced by irradiation with different

parameters.[13–15] Since IPL, a broadband source, with a filtered wavelength ≥ 590 nm, includes the visible and NIR spectra, it is reasonable to consider PBM as a key mechanism [14, 15].

PBM has been used in many areas, such as wound healing, pain release, acne, hair regeneration, anti-inflammation, neurophysiological applications [15]. Some cases took advantage of the indirect effects of PBM; a typical example is in the field of neurophysiology. Several studies have shown that a helmet that blocks the light from being applied directly to the head does not inhibit the beneficial effects of PBM in models of Parkinson's disease [16–18]. Therefore, the PBM theory might be a proper explanation for the indirect effects of light therapies and helpful to understand the effects IPL has on areas to which it is not directly applied.

MGD is a leading cause of dry eye disease, which is a common complaint in eye clinics [19]. Obstruction, telangiectasia, inflammation, and acini atrophy are the main concerns in regard to MGD. Currently, with the theory of PBM that has effects on inflammation, protein synthesis, oxidative stress, PBM might be an adequate solution to MGD and a crucial mechanism of IPL in treating MGD.

With regard to the TBUT results, neither of the two groups had statistically significant improvement simultaneously when MGYSS had improved. In our previous study, we had baseline TBUTs of 6.86 ± 2.69 s and 7.64 ± 2.23 s. We performed IPL and MGX and showed a statistically significant improvement in TBUT [4]. When we looked back to the baseline valued this time, we noticed that 90.3% of the subjects in Group A and 92.3% in Group B had a TBUT of less than 5 s. Furthermore, some of them did not have fluorescein staining with such short TBUTs. This reminded us of a special kind of dry eye condition called short TBUT dry eye.

Short TBUT dry eye is characterized by a TBUT of less than 5 s, with dry eye symptoms. Patients with this condition show no insufficiency in tear production, nor staining of the ocular surface. Simply, any change in the three layers (lipid, aqueous, or mucin) of the tear film would have an influence on the film's stability. To date, there have been several reports on goblet cell reduction, changes in mucin components, chronic inflammation, and allergies, all associated with short TBUT dry eye [20]. MGD, as a chronic disease, is inevitably accompanied by chronic inflammation of the lid margins and ocular surface, which can lead to goblet cell death and mucin abnormalities. In short-term observation, there may not be sufficient time for goblet cells and mucin to recover. In addition, if tear film stability follows the Buckets effect, TBUT will not be prolonged if other layers of the tear film do not recover in time.

And considering that corneal nerves play a key role on ocular surface homeostasis, the central corneal subepithelial nerves (CCSN) were also observed before and after the IPL intervention, and no difference was found. However, given longer observation, there might be interesting and inspiring changes.

In addition, this time, we did not perform MGX after each treatment as usual, as we were interested in observing the indirect effects of IPL, not to be mixed or covered by the effects of MGX. Thus, quality-improved meibum may not be sufficiently secreted onto the ocular surface in time. As a result, there would not be enough time for a better environment to be created for goblet cells and mucin to recover.

There were limitations in this study. First, we used moist fluorescein sodium strips for the TBUT measurements. The components of fluorescein sodium strips may change the characteristics of the tear film, although this is a small effect. Second, we only observed the short-term outcomes. We believe longer observation is necessary especially in TBUT and corneal nerves.

Conclusions

The beneficial effects of IPL did not differ between groups in the short term, with respect to the distance of the treatment application from the lower lid margin. This implies the existence of indirect effects of IPL. Thus, our findings suggest that the IPL beam can be moved to a greater distance from the eyelid margin when treating MGD, to better protect the eye while maintaining the expected treatment outcomes. Additional trials with a larger sample size or across multiple centers are required to gain stronger evidence. Further study is required to compare the long-term effects of different treatment distances.

Declarations

Funding

This work was supported by the National Natural Science Foundation of China 81870629.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yu Cheng, Wenjing Song. The first draft of the manuscript was written by Yu Cheng and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This trial followed the principles of the Declaration of Helsinki and was registered in the Chinese Clinical Trial Registry (ChiCTR1800019160). Approval from the Human Research and Ethics Committee of Peking University First Hospital was attained before enrollment began.

Consent to participate

All participants signed informed consent before any examinations or treatments were performed.

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Tables

Table 1 Demographic information of Group A and Group B

	Randomization Group		
	A: 3-Millimeter Distance	*B: 10-Millimeter Distance*	*p* values
Subjects, n	32	28	/
Age(years),means±standard deviation (range)	36.16±12.92 18~63	36.50±12.23 22~61	0.91
Gender(female/male), n%	18/14, (56.3/43.8) %	19/9, (67.9/32.1) %	0.36
Fitzpatrick Type(/ / /) n%	0/8/18/6, (0/25.0/56.3/18.8) %	0/8/18/2, (0/28.6/64.3/7.1) %	0.42

Table 2 Measurements of variables at each time point

		T0 (Baseline)	T1 (3w after the 1st treatment)	T2 (3w after the 2nd treatment)	T3 (3w after the 3rd treatment)
u-MGYSS	Group A	5.65±3.14	7.09±4.60	9.22±4.76	8.41±4.53
	Group B	4.96±3.44	8.11±4.16	8.71±3.87	9.61±3.73
	p Value	0.35	0.34	0.79	0.19
l-MGYSS		3.13±2.49	3.94±4.03	4.97±4.13	5.53±3.72
	Group A	2.75±3.19	4.14±2.53	5.82±3.20	5.89±4.06
	Group B	0.25	0.44	0.16	0.77
	p Value	8.77±4.90	11.03±6.72	14.19±7.17	13.94±6.93
T-MGYSS		7.71±4.97	12.25±5.87	14.54±5.34	15.50±6.21
	Group A	0.34	0.54	0.83	0.31
	Group B	3.36±1.34	3.99±1.68	3.59±1.28	3.82±1.53
TBUT		3.29±1.88	3.77±1.47	3.16±1.21	3.89±1.38
	p Value	0.63	0.60	0.10	0.57
SPEED		13.78±4.96	/	/	10.41±5.51
	Group A	13.07±3.58	/	/	9.04±4.19
	Group B	0.99	/	/	0.29
	p Value	2482.66±663.65	/	/	2492.20±566.61
Nerve density		2490.61±701.16	/	/	2434.94±477.30
	Group A	0.97	/	/	0.68
	Group B	1.10±1.50	/	/	0.60±0.76
	p Value	1.08±1.32	/	/	0.91±1.04
CFS		0.83	/	/	0.36

	Group A	Group B	*p* Value
	Group A	Group B	*p* Value

Table 3 Change values and rates of variables compared to baseline at each time point

Change values and rates compared to baseline		T1 (3w after the 1st treatment)	T2 (3w after the 2nd treatment)	T3 (3w after the 3rd treatment)
Δu-MGYSS	Group A	1.48±5.01 (26.2%)	3.42±4.36(60.5%)	2.32±4.45(41.1%)
	Group B	3.14±5.07(63.3%)	3.75±5.89(75.6%)	4.64±5.18 (93.5%)
	p Value	0.21	0.81	0.07
Δl-MGYSS		0.68±4.59 (21.7%)	1.87±4.42(59.7%)	2.45±4.23(78.3%)
	Group A	1.39±3.79(50.5%)	3.07±3.42(111.6%)	3.14±3.83(114.2%)
	Group B	0.52	0.25	0.69
ΔT-MGYSS		2.16±8.19(24.6%)	5.29±7.13(60.3%)	4.77±7.27(54.4%)
	p Value	4.54±6.56(58.9%)	6.82±6.77(88.5%)	7.79±6.49(101.0%)
		0.23	0.40	0.10
ΔTBUT	Group A	0.58±1.83(17.3%)	0.25±2.07(7.4%)	0.33±1.85(9.8%)
	Group B	0.34±1.50(10.3%)	-0.09±1.89(-2.7%)	0.62±2.13(18.8%)
	p Value	0.54	0.64	0.59
ΔSPEED			/	-3.38±4.90 (-24.5%)
	Group A	/	/	
	Group B	/	/	-4.04±3.92 (-30.9%)
	p Value	/		0.57
ΔNerve density			/	
		/	/	42.38±637.37 (1.7%)
	Group A	/	/	
	Group B	/		-55.67±631.09 (-2.2%)
ΔCFS			/	0.29
	p Value	/	/	
		/	/	-0.542±1.25 (-49.3%)

	Group A	/	-0.217±1.70 (-21.7%)
	Group B		0.36
	p Value		
	Group A		
	Group B		
	p Value		

Figures

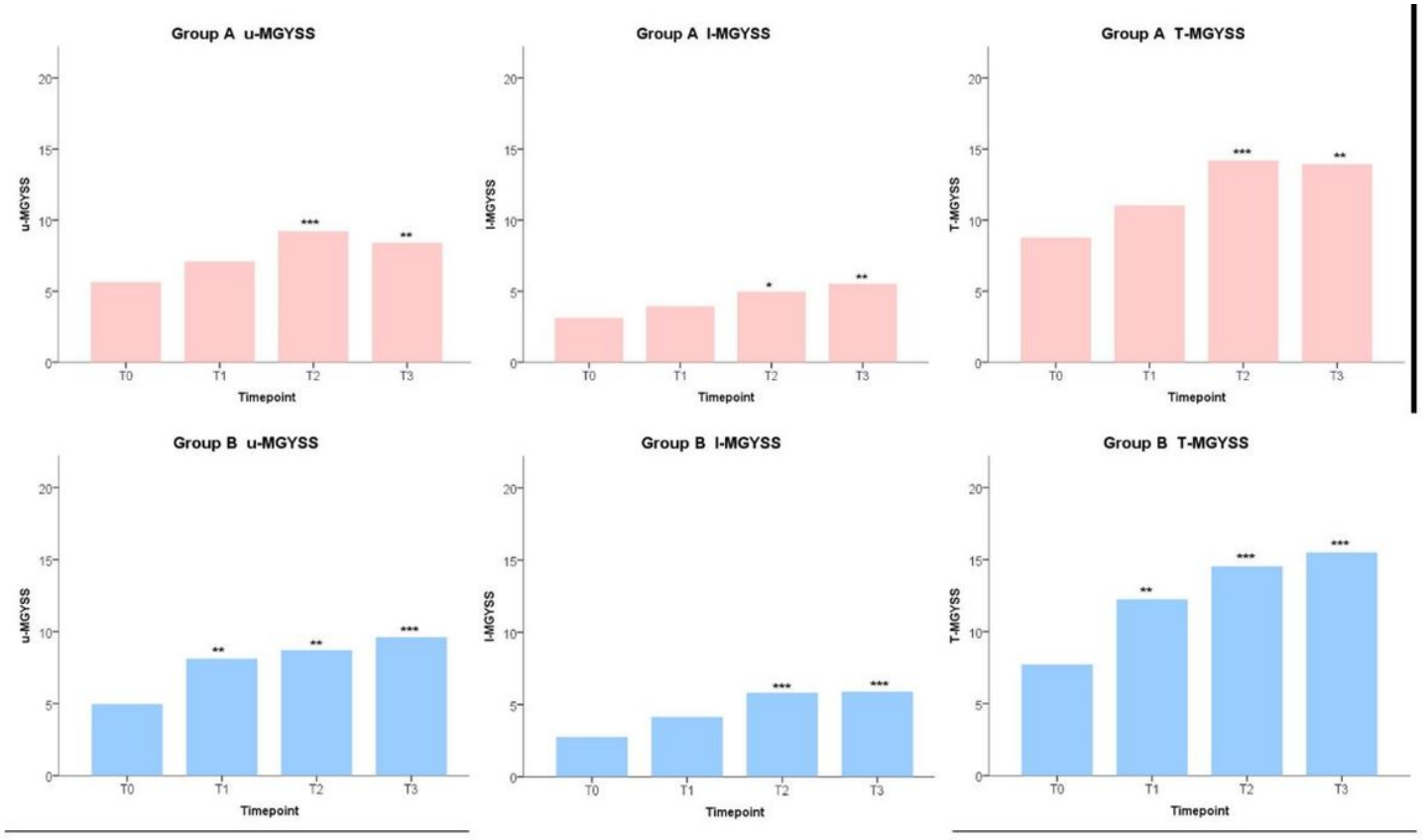

Figure 1

MGYSS at different timepoints in Group A and Group B

The meibomian gland yield secretion scores (MGYSS) were evaluated at baseline (T0) and at 3 weeks after each treatment (T1-T3). The first IPL treatment was performed within 3 weeks after enrollment (T0);

the following two treatments were performed at 3-week intervals. Red bars represent MGYSS of Group A, and blue bars represent MGYSS of Group B. U-MGYSS, l-MGYSS and T-MGYSS are separately presented in each group. MGYSS at each timepoint was compared to baseline and p values are shown by asterisks (*: p<0.05, **: p<0.01, ***: p<0.001)

Abbreviations: MGYSS = meibomian gland yield secretion score; u-/l-/T-MGYSS = meibomian gland yield secretion score of upper eyelids/ lower eyelids/ total of upper and lower eyelids

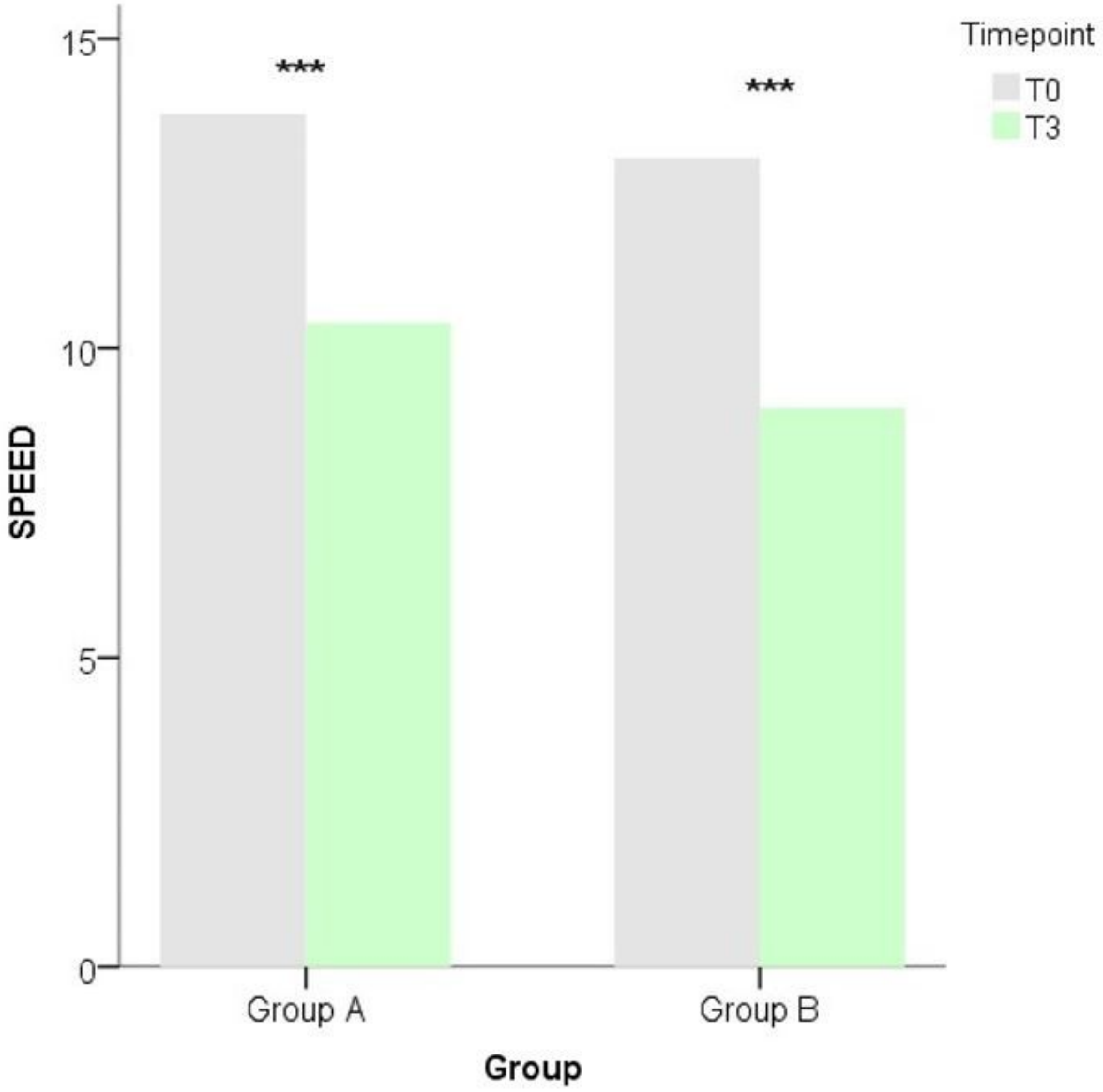

Figure 2

Scores of SPEED before and after three IPL treatments

Standard patient evaluation of eye dryness (SPEED) was assessed at baseline (T0) and at 3 weeks after the third treatment (T3). Both groups had a significant decrease in SPEED (both p<0.001)

Abbreviations: ***, p<0.001. SPEED= Standard patient evaluation of eye dryness