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Efficacy of intense pulsed light and meibomian gland expression treatments in meibomian gland dysfunction

A meta-analysis of randomized controlled trials

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Abstract

Purpose: This review aimed to evaluate the efficacy and safety of intense pulsed light treatment combined with meibomian gland expression treatments in meibomian gland dysfunction.

Methods: We conducted a meta-analysis of randomized controlled trials that compared the efficacy of intense pulsed light treatment and meibomian gland expression treatments in the treatment of dry eye disease. The meibomian gland yielding secretion score was the primary outcome, whereas the secondary outcomes included the Meiboscore, tear breakup time in seconds, standard patient evaluation for eye dryness and corneal fluorescein staining.

Results: This study consisted of 6 trials with 326 patients. Significantly greater improvement was observed in meibomian gland yielding secretion score at 1 month [mean difference (MD): 13.69 (95% CI, 11.98, 15.40)] and at 3 months [MD: 11.03 (95% confidence interval (CI), 10.27, 11.80)], low meibomian gland yielding secretion score at 1 month [MD: 6.92 (95% CI, 5.49, 8.34)] and at 3 months [MD: 6.80 (95% CI, 5.01, 8.59)], up meibomian gland yielding secretion score at 1 month [MD: 6.41 (95% CI, 4.12, 8.70)] and at 3 months [MD: 8.06 (95% CI, 5.70, 10.42)] and tear breakup time at 1 month [MD: 2.38 (95% CI, 1.83, 2.92)] and at 3 months [MD: 1.82 (95% CI, 1.48, 2.19)] in the IPL-MGX group than in the MGX group.

Conclusions: IPL-MGX is safer and more efficacious as compared to the MGX alone in the treatment of patients with meibomian gland dysfunction-related dry eye. We recommend discussing the decision with the ophthalmologist for an appropriate choice.

Abbreviations: CFS = corneal fluorescein staining, CI = confidence interval, DED = dry eye disease, IPLT = intense pulsed light treatment, MD = mean difference, MGD = meibomian gland dysfunction, MGXT = meibomian gland expression treatments, MGYSS = meibomian gland yielding secretion score, RCTs = randomized controlled trials, SPEED = standard patient evaluation for eye dryness, TBUT = tear breakup time.

Keywords: dry eye disease, intense pulsed light, meibomian gland dysfunction, meibomian gland expression

1. Introduction

Dry eye disease (DED) is a multifactorial disease of the ocular surface manifested with several pathophysiological characteristics like loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1] Global mapping of prevalence was undertaken, which revealed the prevalence of DED ranged from 5 to 50%. The prevalence of signs was higher and more variable than symptoms.[2] Most DED cases result from excessive evaporation of the tear film, mainly due to obstructive meibomian gland dysfunction (MGD).[3,4] MGD, being the primary cause of evaporative dry eye, results in an unstable tear film and symptoms such as eye dryness, eye irritation, foreign body sensation, burning, watering, and eye fatigue.[5] MGD is a chronic, diffuse abnormality of the meibomian glands, predominantly characterized by terminal duct obstruction and/or qualitative/quantitative alterations in the glandular secretion.[6] At present, the main treatment methods include the application of a warm compress, the practice of lid hygiene, forced meibum expression, intraductal probing, automated thermal pulsation, dietary supplementation with omega-3 fatty acids, artificial tears, antibacterial drugs, and anti-inflammatory drugs.[7–9] However, these therapies provide limited relief and are generally unsatisfactory. Thus, treatment strategies aiming to prevent progressions may reverse the condition to a certain extent.

QZ contributed equally to this work.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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New treatment modalities and effective management strategies are essential to combat the increased incidence and rapid growth of DED. Intense pulsed light (IPL) is a mature technology in dermatology for the treatment of skin telangiectasia, erythema, pigmentation, aging skin, and other ailments. The therapeutic efficacy of this method is responsible for its widespread application.[10,11] Since then, other ophthalmologists have explored the effectiveness of IPL treatment for MGD/dry eye.[12–15] Recently, the Management and Therapy Subcommittee of the TFOS DEWS II recommended intense pulsed light (IPL) as a second step therapy following education, lid hygiene, and different types of ocular lubricants.[16] Several randomized controlled trials (RCTs) have investigated the efficacy of intense pulsed light treatment (IPLT) and meibomian gland expression treatment (MGXT) in MGD in the past few years.[17–22] However, no meta-analysis has been conducted to portray an overall picture of the efficacy. In this study, we conducted a meta-analysis of RCTs comparing the efficacy of IPLT and MGXT in DED.

2. Materials and Methods

2.1. Inclusion criteria

This study included RCTs to assess the consequences of IPL and MGX in MGD. Trials were required to report the inclusion and exclusion criteria for patients and intervention procedures. RCTs that involved patients undergoing other interventions or not following complete randomization were excluded.

2.2. Search strategy and study selection

The following electronic databases were searched for studies published before July 2020 without language restrictions: PubMed, Embase, Cochrane, Chinese Biomedical Database, and ClinicalTrials.gov registries. The search terms were as follows: intense pulsed light, Dry eye syndrome, meibomian gland expression, warm compress, and MGD. All references in the retrieved articles were scanned to identify other potentially available reports. The initial search identified a total of 83 articles, out of which, 6 were included in the final analysis (Table 1). The ethical approval of the present study is not necessary because this is a meta-analysis, which is based on published literature and does not involve new human participants. The systematic review described has been accepted by INPLASY, an online international prospective register of systematic reviews (registration number is INPLASY 202060069 or DOI number is 10.37766/inplasy2020.6.0069).

2.3. Data extraction

Two reviewers (C.L. and Q.Z) independently screened the eligible studies. If the 2 judges encountered disagreements, they were resolved through discussion with a third reviewer.

2.4. Methodological quality appraisal

Two authors (C.L. and Q.Z.) adopted the "Risk of bias" table of Cochrane Bias tool to evaluate all the biased risks incorporated in the study.[23] "Risk of bias" table includes assessments for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and "other issues."

2.5. Outcomes

The primary outcome measure was the meibomian gland yielding secretion score (MGYSS). The score for the upper eyelid was termed the u-MGYSS and that for the lower eyelid was

Table 1

Characteristics of the randomized controlled trials satisfying the inclusion criteria.

Trial	Inclusion criteria	No. participants or eyes	Mean age (yr)	Intervention
Rong 2017	Age ≥ 18; SPEED II ≥ 6; MGYSS ≤ 12; Fitzpatrick skin type of 1–4	IPL + MGX: 44 eyes Sham IPL + MGX: 44 eyes	27 ± 16.94	IPLT: received 3 consecutive treatments with 14–16 J/cm^2 for 3 mo. Sham IPL: received a placebo therapy with 0J/cm^2 for 3 mo.
Arita 2018	Age ≥ 20; Diagnosis of MGD according to Japanese MGD diagnostic criteria; Fitzpatrick skin type of 1–4	IPL + MGX: 22patients MGX: 20patients	IPL + MGX: 61.0 ± 18.0 MGX: 61.9 ± 12.2	IPL + MGX: IPL + MGX was performed for each eye every 3 weeks for 32 wks. MGX: MGX was performed of each eye every 3 wks for 32 wks.
Rong 2018	Age ≥ 18; SPEED II ≥ 6; MGYSS ≤ 12; Fitzpatrick skin type of 1–4	IPL + MGX: 28 eyes Sham IPL + MGX: 28 eyes	42.17 ± 17.62	IPL + MGX: Received treatments with 14–16 J/cm^2 of IPL + MGX on the upper and lower eyelids for 9 mo. Sham IPL + MGX: received treatments with 0 J/cm^{2}of IPL + MGX on the upper and lower eyelids for 9 mo.
Rong 2018	Age ≥ 18; SPEED II ≥ 6; MGYSS ≤ 12; Fitzpatrick skin type of 1–4	IPL + MGX: 44 eyes Sham IPL + MGX: 44 eyes	46.3 ± 16.9	IPL + MGX: Received treatments with14–16 J/cm^{2}of IPL + MGX on the upper and lower eyelids for 3 mo. Sham IPL + MGX: Received treatments with 0 J/cm^2 of IPL + MGX on the upper and lower eyelids for 3 mo.
Dai 2019	Age ≥ 18; OSDI > 13;	IPL + MGX:76 eyes MGX: 70 eyes	IPL + MGX:41.79 ± 10.71 MGX: 42.23 ± 11.03	IPL + MGX: Received treatments with10–14 J/cm^2 of IPL + MGX on the upper and lower eyelids for 3 mo. MGX: MGX on the upper and lower eyelids for 3 mo.
Yan 2020	Age ≥ 18; SPEED II ≥ 6; Fitzpatrick skin type of 1–4;	IPL + MGX: 120 eyes MGX:120 eyes	IPL + MGX:42.4 ± 14.2 MGX: 41.8 ± 14.1	IPL + MGX: Received treatments with12–15 J/cm^2 of IPL + MGX on the upper and lower eyelids for 9 wks. MGX: MGX on the upper and lower eyelids for 9 wks.

Arita 2018[17] and Rong 2018[21] conducted further crossover intervention after the first endpoint. Only pre-crossover data were used in our study.

IPL = intense pulsed light, MGX = meibomian gland expression, MGD = meibomian gland dysfunction, MGYSS = meibomian gland yielding secretion score, OSDI = Ocular Surface Disease Index, SPEED = standard patient evaluation for eye dryness.

referred to as l-MGYSS. This score reflected meibomian gland function and was estimated using a meibomian gland evaluator. The secondary outcomes included the Meiboscore, tear breakup time (TBUT) in seconds, standard patient evaluation for eye dryness (SPEED), and Corneal Fluorescein Staining (CFS).

2.6. Statistical analyses

All statistical analyses were conducted using Review Manager, version 5.3 (The Cochrane Collaboration, Oxford, United Kingdom). Meta-analysis was performed following the preferred reporting items for systematic reviews and meta-analyses guidelines.[23] For trials that reported crossover data, only the data before crossover was used.

A random-effect model was used to analyze data,[24] assuming that the true effect sizes could vary from study to study. For all variables, the effect size was calculated using the standardized difference in mean values. The standardized difference in mean along with 95% confidence interval (CIs) was computed for each outcome measure from the mean, standard deviation, and sample size. $P < .05$ was considered statistically significant. Heterogeneity was evaluated using The Cochrane Q tests and I^2 tests. Statistical significance was set at $P < .10$ for Cochrane Q tests. Subgroups were analyzed through the pooling of available estimates to obtain similar subsets of patients across trials.

3. Results

3.1. Literature retrieval results

Figure 1 narrates a detailed description of the search and selection process. The search found 83 citations, of which 28 were excluded through a preliminary search and screening of the titles and abstracts. After further consideration of the remaining 58, 52 studies were excluded for the following reasons: 2 not RCTs, 23 not related to MGS or IPL therapy, and 27 without available data. Finally, the meta-analysis incorporated 6 studies.[17–22]

3.2. Study characteristics

The 6 studies reported 334 participants in the IPL group and 326 in the control group. Among these studies, 5 were conducted in China[18–22] and 1 in Japan[17]. These 6 trials were published between 2017 and 2020. The sample sizes ranged from 20 to 120 eyes. The mean age of the patients ranged from 27 to 61 years. The main features of the 6 RCTs are detailed in Table 1.

3.3. Quality assessment results

To elucidate the risk of bias, each study was analyzed using the Cochrane Collaboration Organization tool (Fig. 2).[25] There was no selection bias as allocation concealment was clearly described in the 6 trials. Blinding patients and masking patients were not mentioned in 4 studies.

The follow-up rate of 6 studies exceeded 80%. The results of CFS and MGYSS cannot be used for the meta-analysis because the results are skewed by Rong et al[18] 6 studies have no selective reports. Other biases in the 6 studies were unclear.

3.4. MGYSS

Two of the included trials reported on the MGYSS in IPL and control groups. The outcomes were evaluated after treatment at 1 month and 3 months in the 2 trials.[21,22] These trials were categorized into 1 month and 3 months subgroups in the meta-analysis. A meta-analysis was performed on mean standard deviation values of the 2 studies, revealing that patients with dry eye syndrome who received the intervention of IPL/IPL + MGX had significantly higher MGYSS as compared to those in control groups at 1 month [mean difference (MD): 13.69 (95% CI, 11.98, 15.40)] or at 3 months [MD: 11.03 (95% CI, 10.27, 11.80)]. No heterogeneity across trials was observed at 1 month ($I^2 = 17\%$, $P = .27$) and 3 months ($I^2 = 0\%$, $P = .69$) post-treatment. A difference was observed between the 2 subgroups ($I^2 = 87.1\%$, $P = .005$). (Fig. 3)

3.5. L-MGYSS

l-MGYSS was measured in 2 RCTs at 1 month and 3 months after treatment.[21,22] The IPLT group exhibited significantly greater l-MGYSS improvements at 1 month [MD: 6.92 (95% CI, 5.49, 8.34)] and at 3 months [MD: 6.80 (95% CI, 5.01, 8.59)]. No heterogeneity was observed across trials (1 month: $I^2 = 0\%$, $P = .70$; 3 months: $I^2 = 0\%$, $P = .45$). Furthermore, there was no significant difference between the 2 subgroups ($I^2 = 0\%$, $P = .92$). (Fig. 4)

3.6. u-MYGSS

u-MGYSS was examined in 2 RCTs at 1 month and 3 months after treatment.[21,22] The IPLT group demonstrated significantly greater u-MGYSS improvements at 1 month [MD: 6.41 (95% CI, 4.12, 8.70)] and at 3 months [MD: 8.06 (95% CI, 5.70, 10.42)]. No heterogeneity was observed across trials (1 month: $I^2 = 0\%$, $P = .99$; 3 months: $I^2 = 3\%$, $P = .31$). Furthermore, no difference was obtained between the 2 subgroups ($I^2 = 0\%$, $P = .32$). (Fig. 5)

3.7. Meiboscore

Two RCTs included in this meta-analysis assessed the meiboscore at 1 month and 3 months after treatment.[17,22] No difference was documented at 1 month [MD: 0.02 (95% CI,–0.21, 0.26)] or at 3 months [MD: 0.00 (95% CI,–0.22, 0.23)] after treatment. No heterogeneity was observed across trials (1 month: $I^2 = 0\%$, $P = .74$; 3 months: $I^2 = 0\%$, $P = .97$). Furthermore, no difference was witnessed between the 2 subgroups ($I^2 = 0\%$, $P = .90$). (Fig. 6)

3.8. TUBT

TBUT was analyzed in 5 RCTs. Five trials reported the outcome at 1 month[17,18,20–22] and 4 trials documented the outcome at 3 months after treatment.[17,18,20,21] These trials were categorized as 1 month and 3 months subgroups in the meta-analysis. The IPLT group substantiated significantly greater TUBT improvements at 1 month [MD: 2.38 (95% CI, 1.83, 2.92)] and at 3 months [MD: 1.82 (95% CI, 1.48, 2.19)]. There was no heterogeneity across trials (1 month: $I^2 = 34\%$, $P = .20$; 3 months: $I^2 = 0\%$, $P = .91$). Furthermore, no difference was noted between the 2 subgroups ($I^2 = 0\%$, $P = .46$) (Fig. 7).

3.9. SPEED

SPEED was determined in 4 RCTs. Four trials narrated the outcome at 1 month[18,20–22] and 4 trials reported the outcome at 3 months after treatment.[18,20–22] These trials were classified as 1 month and 3 months subgroups in the meta-analysis. No difference was established at 1 month [MD:–1.08 (95% CI,–2.59, 0.44)] or at 3 months [MD:–1.07 (95% CI,–2.19, 0.66)] after treatment. No heterogeneity was perceived across trials (1 month: $I^2 = 45\%$, $P = .14$; 3 months: $I^2 = 0\%$, $P = .69$). Furthermore, no difference was observed between the 2 subgroups ($I^2 = 0\%$, $P = .99$) (Fig. 8).

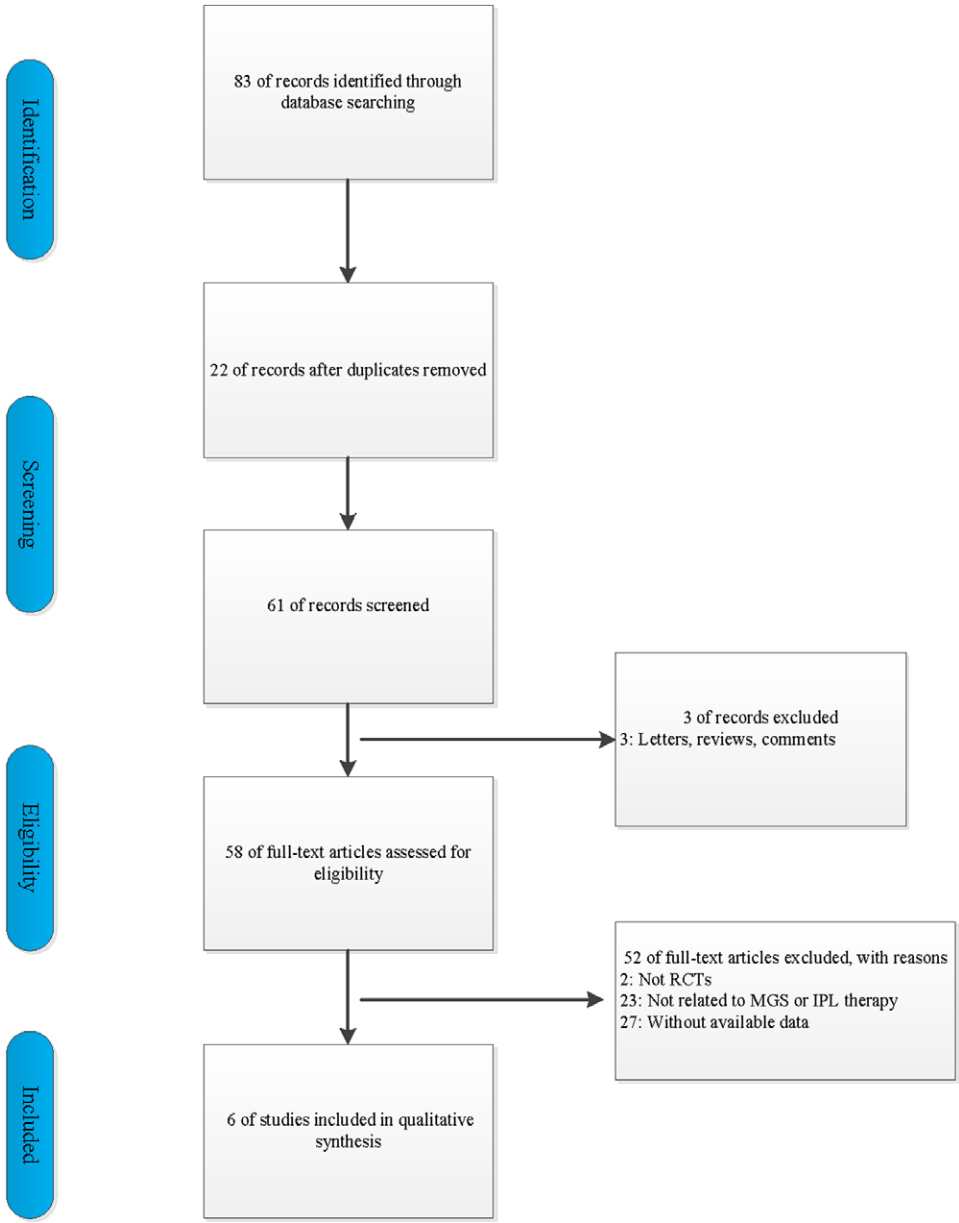

Figure 1. Flow chart illustrating the study selection procedure. This meta-analysis included 6 RCT studies. RCT = randomized controlled trial.

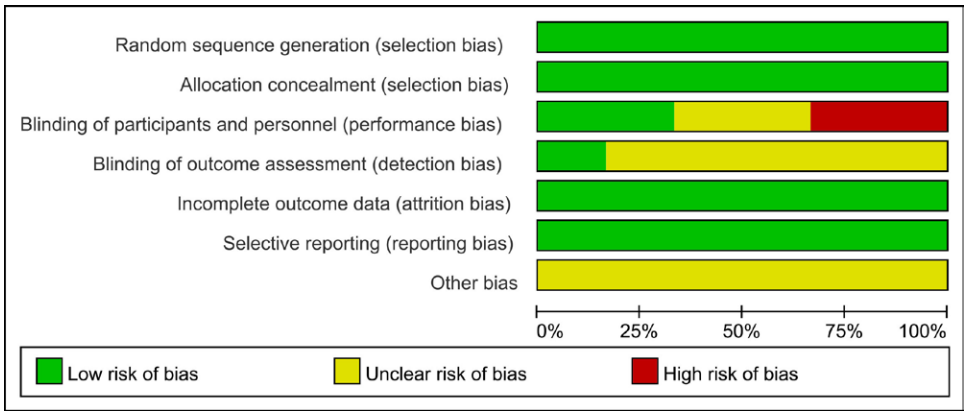

Figure 2. Risk of bias assessment of the included studies.

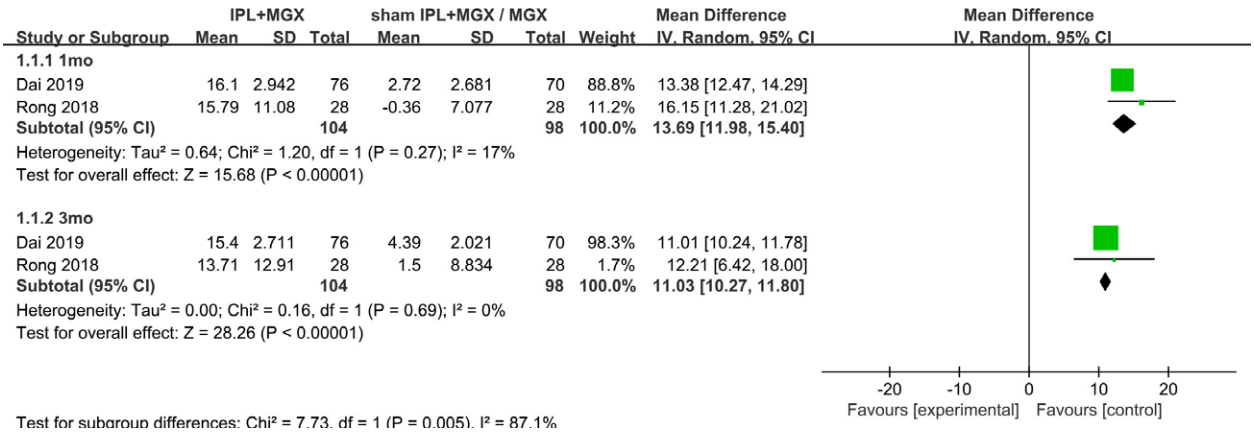

Figure 3. Forest plot comparing the IPL and MGX treatment groups illustrating post-treatment MGYSS at 1 month and 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation, MGYSS = meibomian gland yielding secretion score.

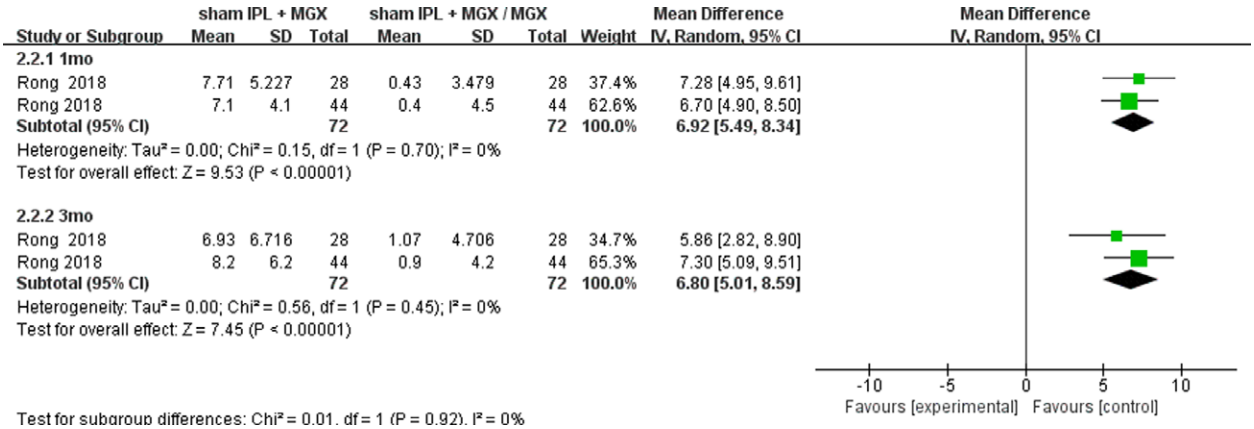

Figure 4. Forest plot comparing the IPL and MGX treatment groups highlighting post-treatment l-MGYSS at 1 month and at 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation, u-MGYSS = up meibomian gland yielding secretion score.

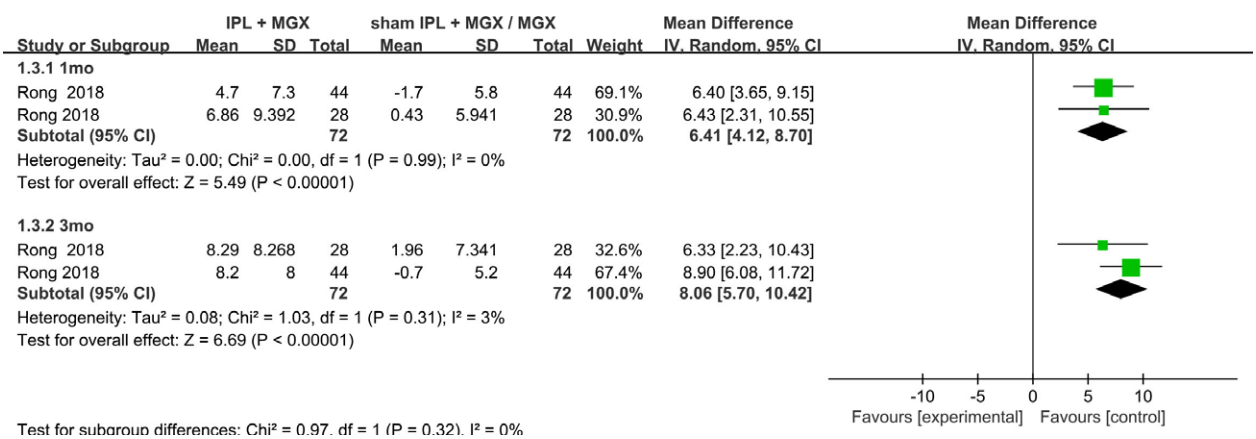

Figure 5. Forest plot comparing the IPL and MGX treatment groups reflecting post-treatment u-MGYSS at 1 month and 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation, l-MGYSS = low meibomian gland yielding secretion score.

3.10. CFS

CFS was measured in 4 RCTs. Three trials detailed the outcome at 1 month [17,20,21] and 4 trials documented the outcome at 3 months after treatment.[17,19–21] These trials were categorized into 1 month and 3 months subgroups in the meta-analysis. There was no difference at 1 month [MD:–0.58 (95% CI,–1.31, 0.20)] or at 3 months [MD:–0.30 (95% CI,–1.06, 0.47)] after treatment. Heterogeneity was observed across trials (1 month: $I^2 = 69\%$, $P = .04$; 3 months: $I^2 = 83\%$, $P = .0005$). Moreover, there was no difference between the 2 subgroups ($I^2 = 0\%$, $P = .64$) (Fig. 9).

4. Discussion

We observed the effectiveness of IPLT + MGXT over the traditional MGX in improving MGYSS, l-MGYSS, u-MGYSS, TBUT.

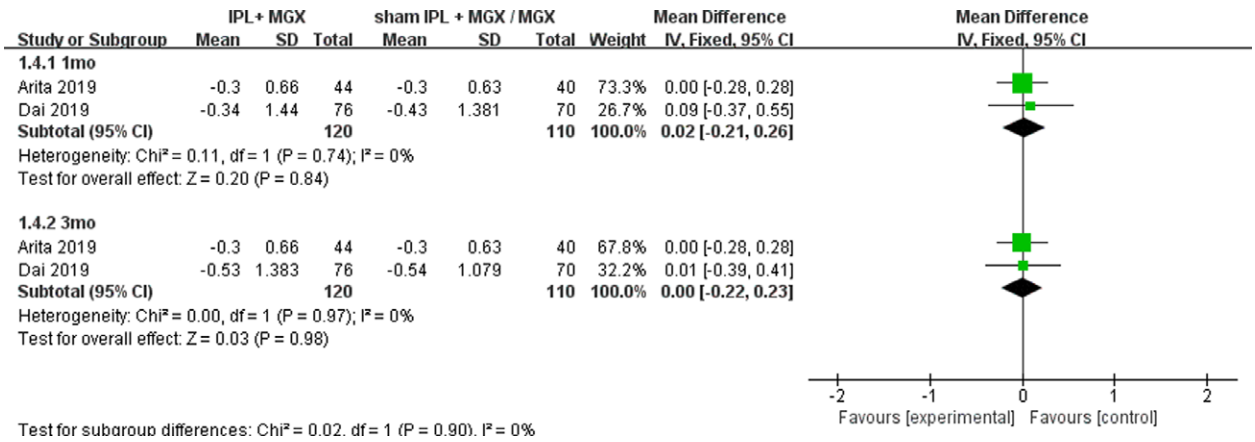

Figure 6. Forest plot comparing the IPL and MGX treatment groups illustrating post-treatment meiboscore at 1 month and 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation.

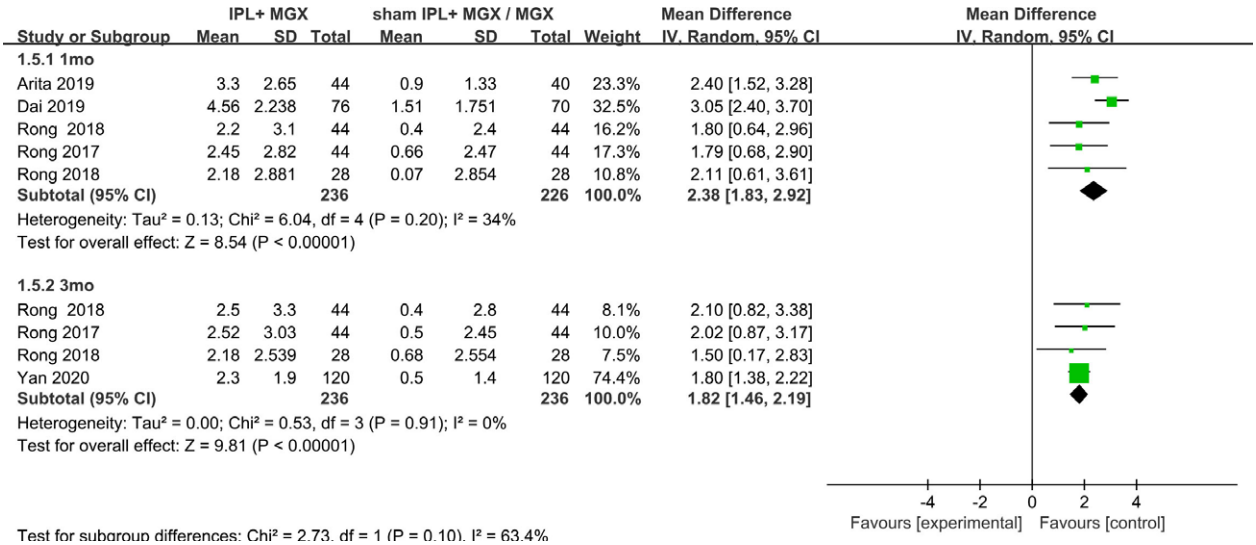

Figure 7. Forest plot comparing the IPL and MGX treatment groups indicating post-treatment TUBT at 1 month and 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation, TBUT = tear breakup time.

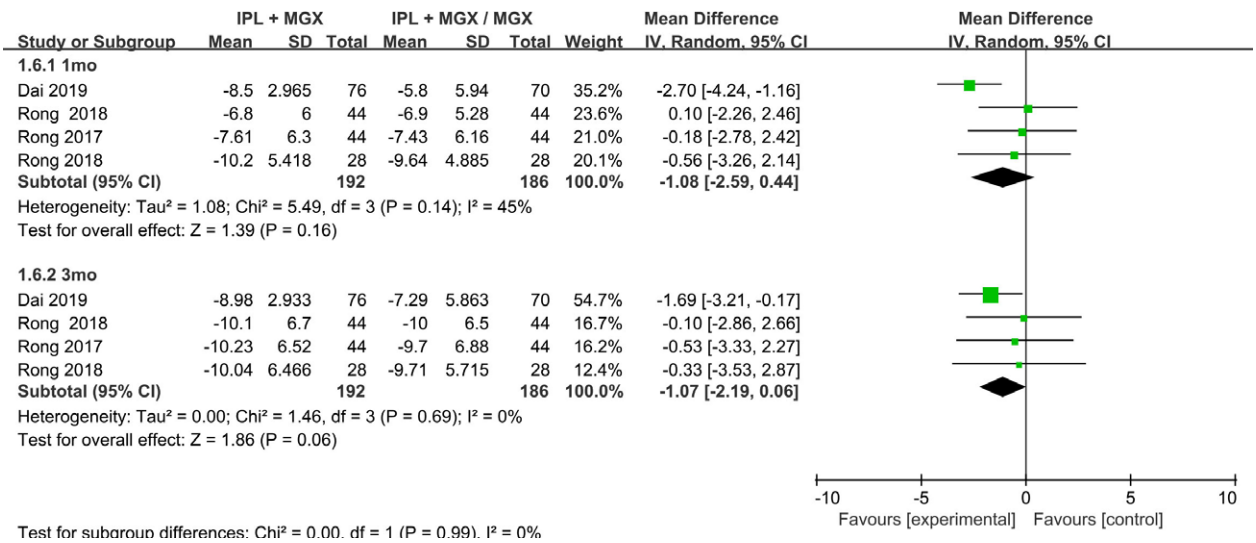

Figure 8. Forest plot comparing the IPL and MGX treatment groups illustrating post-treatment SPEED at 1 month and 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation, SPEED = standard patient evaluation for eye dryness.

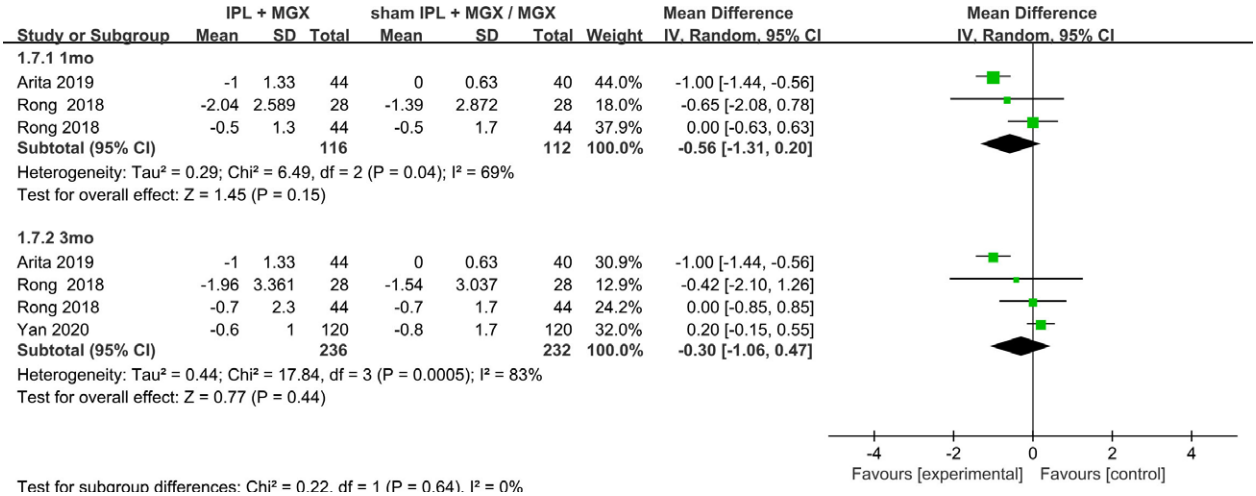

Figure 9. Forest plot comparing the IPL and MGX treatment groups showing post-treatment CFS at 1 month and 3 months. CI = confidence interval, IPL = intense pulsed light, MGX = meibomian gland expression, SD = standard deviation, CFS = corneal fluorescein staining.

Compared to MGX, IPL combined with MGX is convenient, safe, and effective for the treatment of MGD-related dry eyes. Besides, the efficacy and maintenance time of IPL combined with MGX is better than MGX alone.[17–22] One RCT included in our study validated that the effects of IPL-MGX on TUBT, plugging, vascularity, CFS score, and meibum grade in MGD can be maintained for 32 weeks.[17] Another RCT showed that the l-MGYSS and SPEED scores of patients receiving IPL treatment could be significantly ameliorated until 9 months after treatment.[21] Furthermore, a retrospective study indicated a significant improvement in TUBT and post-treatment satisfaction with the degree of dry eye syndrome symptoms for up to 3 years in patients treated with IPL-MGX [26]. In terms of safety, no irreversible eyelid skin damage, anterior segment inflammatory reaction, iris depigmentation, ocular surface or fundus damage, visual acuity damage, and high intraocular pressure were not experienced in these studies,[17,18,20,22] whereas, Bei Rong et al[21] reported 5 patients had mild pain, burning during the IPL treatment.

The average annual direct cost of treating DED patients in the United States is US$783, with a range of US$757 to US$809.[27] The results from a study involving 6 European countries (France, Germany, Italy, Spain, Sweden, and the United Kingdom) claimed that the total annual medical costs for treating 1000 DED patients ranged from US$2,70,000 in France to US$1.1 million in the United Kingdom [28] Researchers from the Singapore National Eye Centre estimated the cost data of 54,052 patients and found that the total annual expenditure for dry eye treatment in 2008 and 2009 exceeded US$1.5 million.[29] The severity of MGD dictates the effect of treatment; henceforth, the annual cost of IPL treatment for different patients varies greatly. We make joint decisions by considering relevant factors (including the convenience of treatment time, the timing of intervention, etc), which will help patients by improving the therapeutic outcome and reducing treatment costs.

Except for the heterogeneity in the CFS trial, our meta-analysis results substantiate the absence of heterogeneity among the trials. To investigate the influence of individual studies on the pooled estimates, each study in the meta-analysis was excluded in turn utilizing leave-1-out cross-validation. We observed that the heterogeneity of the CFS test came from the article by Rong et al[20] The source of heterogeneity was primarily attributed to the study population, selection criteria, and differences in treatment. For instance, first, the average age of trial participants ranged from 27 to 61 years. The age range was large, and the research subjects involved young people and the elderly, which was responsible for the differences in the results of different trials. Second, the inclusion criteria for the included trials were different. One trial followed 4 inclusion criteria, while other trials mentioned 2 to 4 inclusion criteria. Third, there was variation in the trial intervention methods used in the control group. For example, some trials employed sham IPL combined with MGX, whereas some trials used only MGX. Finally, the energy of IPL in the included trials ranged from 12 to 16 J/cm^2 and the frequency also varied. Moreover, the upper eyelid and lower eyelid were treated simultaneously in this article by Rong et al[20]

Nevertheless, this meta-analysis has some limitations that should be taken into consideration. First, the analyzed trials had significant differences regarding the characteristics of the patients. The mean age of the trial participants was 27 to 61 years and the energy of IPL in the included trials ranged from 12 to 16 J/cm^2. All these may affect the efficacy of IPL in the treatment of MGD. Second, after sensitivity analysis, the difference in corneal fluorescein staining between the 2 groups was unstable. Therefore, this result should be interpreted with caution. Finally, the included trials compared 2 treatments for 3 months only. However, other non-RCT demonstrated that the effects of IPL may last for 3 years.[26]

In conclusion, this systematic review and meta-analysis indicate that IPL-MGX is more efficacious, which improves MGYSS, l-MGYSS, u-MYGSS, and TUBT than the MGX alone. Furthermore, this meta-analysis of 6 RCTs suggests the safety of IPL in the treatment of patients with MGD-related dry eye. Therefore, we recommend discussing the decision with the ophthalmologist to make an appropriate choice.

Author contributions

Data curation: Qi Zhou.
Formal analysis: Qi Zhou.
Investigation: Zi-Qing Gao.
Methodology: Zi-Qing Gao.
Writing – original draft: Chao Liu, Zi-Qing Gao.
Writing – review & editing: Chao Liu.

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