Interplay Between Dermatology and Ophthalmology: a Systematic Review and Meta-Analysis Of Intense Pulsed Light Therapy for Meibomian Gland Dysfunction

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ABSTRACT

OBJECTIVES

To examine, through a meta-analysis, the effectiveness of intense pulsed light therapy (IPL) in the treatment of dry eye symptoms.

METHODS

This study followed the PRISMA statement guidelines. Literature sources included MEDLINE, Embase, Cochrane Library and meeting abstracts from COS, ARVO, the American Academy of Optometry and the American Academy of Ophthalmology. Articles underwent 3 stages of screening before data extraction and meta-analysis.

RESULTS

The search initially identified 495 studies; 52 remained after title screening, 23 remained after abstract screening, and 8 progressed to data extraction. Meta-analysis indicated a significant increase in tear break-up time (TBUT) post-IPL in the less than 1-month follow-up (Standard Mean Difference (SMD)=1.45; CI:[0.33, 2.57]), 1.5-2-month follow-up (SMD=2.08; CI:[1.14, 3.01]), and 3-month follow-up (SMD=3.28; CI:[2.78, 3.78]) groups, and no significant change in TBUT in either the 6-month follow-up (SMD=1.90; CI:[-0.18, 3.98]) or 12-month follow-up from a single study (SMD=0.0; CI:[-0.48, 0.48]) groups. Meta-analysis also indicated a significant increase in Schirmer's test values during the less than 1-month (SMD=0.91; CI:[0.50, 1.31]) and 6-month (SMD=0.65; CI:[0.25, 1.04]) follow-up periods, and no significant change in Schirmer's test values during the 1.5–2 month follow-up period (SMD=0.41; CI:[-0.93, 1.75]).

CONCLUSIONS

The results suggested a significant increase up to 5 months and no significant change at 6 months post-IPL for TBUT. They also suggested a significant increase in Schirmer's test values during the less than 1-month and 6-month follow-up periods, and no significant change in Schirmer's test values during the 1-month follow-up period. Ultimately, IPL seems to be a promising therapy for dry eye symptoms, but future studies with longer follow-up periods are needed.

KEYWORDS:

Intense pulsed light therapy, dry eye, dermatology, ophthalmology, systematic review, and meta-analysis

FUNDING

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Intense pulsed light therapy (IPL) is a type of photodynamic therapy that uses incoherent broad-spectrum light with wavelengths ranging from 500 to 1200 nm.[1] Until recently, IPL has mainly been used in the treatment of dermatological conditions, including but not limited to cosmetic dermatological procedures, treatment of acne, rosacea, psoriasis, and non-melanoma skin cancers.[2-6] Although some side effects can occur (such as blistering of the skin, hypopigmentation, and hyperpigmentation), IPL is generally considered to be a safe treatment option, as harmful ultraviolet radiation in wavelengths ranging from 10 to 400 nm is not used.[6] IPL has also been shown to be effective in treating evaporative dry eye (EDE).

Meibomian glands line the margins of the upper and lower eyelids, and are responsible for producing the lipid component of the tear layer which prevents its evaporation. These glands can be blocked due to a variety of causes, including infrequent blinking, staring at a computer screen for long durations, rosacea, psoriasis, dermatitis of the face, certain medications, and prolonged use of contact lenses.[7-9] Dry eye symptoms include a gritty sensation in the eyes, excessive tearing, blurry or fluctuating vision, and photosensitivity. These symptoms can have a significant negative impact on an individual's quality of life.[10]

The effectiveness of IPL in dry eye disease (DED) is an important topic to explore. Many individuals suffer from dry eye, and some studies estimate that up to 36% of dry eye cases are caused by blocked Meibomian glands. Thus, it is important to study this topic and explore the overall effectiveness of IPL in treating DED. An improved understanding of IPL and its use in treating DED and EDE can allow practitioners to have a greater array of treatment options to choose from when deciding how to manage a patient's dry eye symptoms. Although some previous studies have examined the effectiveness of IPL in treating DED and EDE, to our knowledge, there has been no systematic review or meta-analysis of the literature available on this topic.

The objective of this study was to systematically and comprehensively search for and consolidate all of the current literature regarding the effectiveness and feasibility of IPL as a treatment option for DED.

METHODS

This systematic review and meta-analysis was conducted following the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) Statements. Several databases and grey literature sources were searched to find literature relevant to this topic. The databases searched included MEDLINE (OVID®), Embase, and Cochrane Library. The databases were searched using the terms "intense pulsed light", "intense pulsed light therapy", "dry eye disease", "keratoconjunctivitis sicca", "keratitis sicca", and "dry eye syndrome". The searches were modified as needed to comply with the unique syntax and search terminology/requirements of each individual database. Furthermore, synonyms for the search headings were compiled with the help of an information specialist. OVID® AutoAlerts were set up to send monthly updates regarding any new literature until June 1, 2020, and monthly updates were also performed using the Cochrane Library database.

Grey literature was found by searching the meeting abstracts from the Canadian Ophthalmological Society, the Association for Research in Vision and Ophthalmology, the American Academy of Optometry and the American Academy of Ophthalmology for the years 2003 to 2009.

Inclusion/Exclusion Criteria

Inclusion criteria for the systematic review and meta-analysis included studies related to dry eye treatment outcomes with the use of IPL. Study designs included in the review were economic studies, comparative studies, observational studies, cohort studies, case series, randomized control trials, multi-center studies, retrospective studies, prospective studies, clinical trials, and interventional studies. Multiple study designs were included because there was a paucity of studies available on the topic and, if we had limited the analysis to randomized controlled trials, we would have had a very limited number of studies to analyze. With regard to the exclusion criteria, studies with a sample size of less than 20 eyes, non-English studies, and studies on non-human subjects were excluded. There were no restrictions placed on the country in which the study was performed, the follow-up period or the number of IPL treatments received (as long as at least one IPL treatment was received).

After all of the studies were compiled, the literature was imported into DistillerSR software (Evidence Partners, Ottawa, Ontario, Canada), which is used to conduct systematic reviews. Once imported into DistillerSR, duplicate studies were removed, and studies proceeded to the screening process, including title screening, abstract screening, and full-text screening.

Screening

Screening of the studies was conducted in three stages with the use of DistillerSR. The studies were independently reviewed by two reviewers (RS, GS), and Cohen's kappa coefficient was computed to determine the level of agreement between the two reviewers at each stage of screening. Disagreements with regard to inclusion/exclusion of certain studies were addressed by the two reviewers through discussion. If a consensus could not be reached, a third author (MM) intervened to provide a decision.

The three stages of screening were title screening, abstract screening, and full-text screening. Detailed screening questions are provided in the supplementary material (Appendix A). During the title screening stage, studies that seemed irrelevant to the topic were excluded. During the abstract screening stage, literature that seemed irrelevant to the study were excluded. If the abstract was not available in DistillerSR (due to occasional errors in importing the studies), the studies were found through an additional search (on PubMed) and the abstracts were analyzed. During the full-text screening stage, studies that did not have data pertaining to the study (TBUT, Schirmer test values, Standardized Patient Evaluation of Eye Dryness (SPEED) score, Ocular Surface Disease Index (OSDI), or follow-up period) were excluded from the final analysis.

Study Quality

Once full-text screening was completed, the study quality of the remaining literature was assessed using a modified Downs and Black Checklist.[11] The features from the studies used to assess their quality were reporting, external validity, internal validity (bias and confounding factors), and power. Studies were scored out of 28 and were classified as either poor, fair, good, or excellent quality if they received scores of ≤14, 15-19, 20-25, or 26-28, respectively.

Data Extraction

Data extraction of the studies that progressed through full-text screening was conducted by one investigator (RS). Information that was extracted from the studies included study year, design, location, number of patients and eyes, mean age of the patients, subjective dry eye symptom measurements (such as SPEED score and OSDI), objective dry eye symptom measurements (including Schirmer test, corneal fluorescein staining score (CFS), Meibomian gland yielding secretion score (MGYSS), and tear break-up time (TBUT), and other miscellaneous information such as patient Fitzpatrick skin types. TBUT was used in all of the studies, and provided an objective measure of the change in dry eye signs. All but two studies also assessed either the SPEED score or the OSDI, which provided a subjective measure of the change in dry eye symptoms from the patients themselves.

Meta-Analysis

Once data extraction was completed, the statistical/meta-analysis was completed by one investigator (MM). The meta-analysis portion of this study was conducted with STATA 15.0 (STATA Corporation, College Station, TX). To examine continuous scale outcomes including mean values, the standardized mean difference (SMD) was calculated as the treatment effect or effect size. The SMD represents the mean difference standardized for variances across all studies. Any SMD value greater than zero denotes a benefit. To calculate the SMD, the mean pre- and post-treatment values for each outcome measure were divided by the standard deviation for that same outcome measure for each study. Weights were assigned to each SMD according to the inverse of its variance, and the average was computed. The SMD in each study was pooled with a fixed- or random-effect model based on heterogeneity. The Inverse Variance (I-V) method was used to compute a fixed-effect model and the DerSimonian and Laird (D+L) method was used to compute a random-effects model. Furthermore, a Z-value was computed to test the null hypothesis, which was a treatment effect of zero, to test for heterogeneity.

Finally, heterogeneity was determined using the I^2 value, which indicated the extent of variation across studies due to heterogeneity rather than chance.[12] A chi-squared test was used to examine for heterogeneity between the studies, and assessed whether the observed between-studies differences were due to chance only. A large chi-squared statistic and a low p-value relative to its degree of freedom provided evidence of heterogeneity.

Publication Bias

The potential presence of publication bias was assessed by the examination of funnel plots. Funnel plots for the TBUT and Schirmer's test values were assessed.

RESULTS

Search Results

The initial search identified 495 studies, and 413 studies remained after duplicates were removed. These stud-

ies were then subjected to title screening (level one screening). After both reviewers screened these studies, 361 studies were excluded, leaving 52 studies that progressed to abstract screening (level two screening). During abstract screening, 29 studies were removed because they did not provide data on the effectiveness of IPL in patients with dry eye, leaving 23 studies that progressed to full-text screening (level three screening). During full-text screening, studies were examined to ensure that they met the inclusion criteria. Studies at this stage were also assessed to see if they included relevant data and statistics that could be extracted and used in the meta-analysis. During this stage, 15 studies were removed for the following reasons: eight studies for wrong intervention, five studies for wrong study design, and two studies for having too small of a sample size. Therefore, once full-text screening was completed, eight studies remained.[13-20] The quality check process revealed that four studies were fair quality, four were good quality, and no studies were poor or excellent quality (Appendix B). Once the quality check was completed, these eight studies progressed to the data extraction stage. The results of the screening process are summarized in Figure 1. The kappa statistics, which were calculated before conflict resolution, for levels one, two, and three of screening were 0.82, 0.66, and 0.96 respectively.

Study Characteristics

The eight studies that remained (published between 2014 and 2019) progressed to data extraction and meta-analysis. Of the eight studies, two were clinical trials (including one randomized clinical trial), five were prospective interventional studies (including two prospective, randomized, double-masked, controlled studies, one open-label prospective study, one prospective, double-masked, paired-eye, placebo-controlled study and one prospective single site, interventional study), and one was a retrospective noncomparative interventional case series. In all eight studies, the intervention was IPL. With respect to outcome measures, all eight studies examined TBUT, four examined OSDI, five examined the SPEED score, two examined Schirmer's test values, two looked at MGYSS, and one examined CFS values. The number of IPL treatments per subject and the interval between treatments varied among the studies, from 3 to 4 treatments at 2- to 6-week intervals. The study characteristics are summarized in Appendix C.

Main Outcomes

Impact of Intense Pulsed Light (IPL) Therapy Evaluated in terms of TBUT

All eight studies examined reported TBUT values at various follow-up periods, ranging from 28 days to 1 year post-IPL. Figure 2 shows a forest plot that presents the change in TBUT values post-IPL stratified by follow-up periods. Significant heterogeneity was found between the five studies that evaluated follow-up at less than 1 month (I^2 = 97.0%), the five studies that evaluated follow-up at 1.5 – 2 months (I^2=93.1%), and the two studies that evaluated follow-up at 6 months (I^2 = 96.8%). After we examined the forest plot for TBUT, the meta-analysis

results indicated a significant increase in TBUT after IPL in the less than 1-month follow-up (SMD = 1.45; CI: [0.33, 2.57]), 1.5-2-month follow-up (SMD = 2.08; CI: [1.14, 3.01]), and 3-month follow-up (SMD = 3.28; CI: [2.78, 3.78]) groups, and no significant change in TBUT in the 6-month follow-up (SMD = 1.90; CI: [-0.18, 3.98]) or 12-month follow-up (SMD = 0.0; CI: [-0.48, 0.48]) groups. Therefore, the results suggested a significant increase in TBUT up to 5 months and no significant change in TBUT in dry eye patients at 6 months after IPL treatment.

Impact of Intense Pulsed Light Therapy Evaluated in terms of Schirmer's Test

Three of the studies examined reported Schirmer's test values at various follow-up periods, ranging from 15 days to 32 weeks. Figure 3 depicts the change in Schirmer's test values post-IPL stratified by the follow-up period. Significant heterogeneity was found between the two studies that evaluated follow-up at 1.5-2 months (I^2=95.5%). Our meta-analysis results indicated a significant increase in Schirmer's test values during the less than 1-month (SMD = 0.91; CI: [0.50, 1.31]) and 6-month (SMD = 0.65; CI: [0.25, 1.04]) follow-up periods, and no significant change in Schirmer's test values during the 1.5-2-month follow-up period (SMD = 0.41; CI: [-0.93, 1.75]). However, only one study discussed 6-month follow-up, and therefore more studies are required to make concrete conclusions.

Publication Bias

The funnel plots for the studies that examined TBUT and Schirmer's test values post-IPL are shown in Figures 4 and 5, respectively. The presence or absence of publication bias was assessed using a funnel plot, as asymmetry is observed when publication bias is present. Since the studies appear to be distributed relatively symmetrically in the funnel plots, publication bias was not considered to be present.

DISCUSSION

Dry eye disease has been shown to be a chronic problem, with significant implications for quality of life.[21] The treatment of certain dermatological conditions, such as acne rosacea, with IPL has been shown to result in a decrease in dry eye symptoms.[21] Through this systematic review and meta-analysis, we were able to examine the efficacy of IPL in the treatment of dry eye. Interestingly, the two studies that analyzed the 1.5-2-month follow-up presented SMDs on opposite ends of the spectrum. This could possibly be due to the high heterogeneity between the studies. Our meta-analysis results indicated a significant increase in TBUT up to 5 months post-IPL and no significant change in TBUT at 6-months post-IPL. The reason for this increase in TBUT is likely due to the increased meibum content in the tear layer. After IPL therapy, the Meibomian glands are better able to secrete the components necessary for the tear layer to be fully functional. Therefore, the tear layer is more stable and takes a longer time to break up, resulting in increased TBUT values. Regarding the time course of the results, we feel that patients receiving IPL are likely to show gradual increases in TBUT over time. This is because after being subjected to IPL, the Meibomian glands must secrete meibum, which then needs to get incorporated in the tear layer. This process is unlikely to happen instantaneously. Furthermore, a significant increase in Schirmer's test values was seen at less than 1 month and at 6 months post-IPL. Additional high-quality randomised controlled trials would be beneficial for making a solid inference.

The exact mechanism of the improvement of dry eye symptoms after IPL is still unclear. A possible explanation is that IPL prevents the transmission of inflammatory mediators to the ocular structures. For instance, many patients who experience MGD suffer from acne rosacea of the face. This condition often leads to the production of inflammatory mediators which can travel to the structures of the eye via various pathways, such as through the facial artery. When patients undergo IPL, this causes thrombosis of superficial blood vessels which can prevent the transport of inflammatory mediators to the eye, ultimately reducing the inflammation of the Meibomian glands.[21, 22] Another potential explanation for why IPL is effective in treating dry eye is that IPL increases the temperature of the meibum which allows it to remain in a more liquid/less viscous state. This allows the meibum to better distribute itself over the surface of the eye, resulting in a better-quality tear layer which has a slower rate of evaporation.[21, 23] Other possible explanations include the fact that IPL may reduce epithelial turnover, the use of IPL in the periocular areas can prevent the blocking of Meibomian glands by excess epithelial cells, and IPL can supress matrix metalloproteinase (an inflammatory mediator that is known to contribute to dry eye symptoms).[13]

When we were conducting this study, some limitations became apparent. First, any meta-analysis of observational studies can be influenced by biases present in the papers that are analyzed.[24, 25] For instance, the results of the in-

cluded studies could have been influenced by other factors such as the prevalence and/or severity of dermatologic conditions (such as acne rosacea), the presence of diabetes, smoking history, occupation/screen usage, sex, age, allergies, and contact lens use.[26–31] Second, some studies contained limited information on astigmatism, visual acuity, Fitzpatrick skin type, patient ethnicity, and other factors that may predispose patients to dry eye symptoms or impact the effectiveness of IPL. Despite these limitations, and potentially others, we believe that our systematic review and meta-analysis accurately summarizes the current state of knowledge regarding the use of IPL in the treatment of dry eye.

In conclusion, IPL appears to be a promising therapy in the treatment of dry eye. This systematic review and meta-analysis shows that IPL tends to result in a significant improvement of dry eye symptoms in the short term. We recommend that future studies include larger sample sizes and longer follow-up periods to further evaluate the efficacy and long-term effectiveness of IPL. ●

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None of the authors involved with this paper have any conflicts of interest to disclose. We did not receive any funding for this study.

APPENDICES

Appendix A: *Screening questions for each stage of screening as well as Cohen's kappa values for each screening stage.*

Interplay Between Dermatology and Ophthalmology: A Systematic Review and Meta-Analysis on Intense Pulsed Light Therapy for Meibomian Gland Dysfunction

STAGE 1
Screening Question: Does the study look at intense pulsed light therapy AND its effect on Meibomian gland dysfunction or dry eye symptoms?

Cohen's Kappa Value: 0.82

STAGE 2
Screening Question: Does the study appear to have relevant data on the usage of intense pulsed light therapy in the treatment of Meibomian gland dysfunction or dry eye symptoms?

Cohen's Kappa Value: 0.66

STAGE 3
Screening Question: Does the study have statistics pertaining to the effectiveness of intense pulsed light therapy in the treatment of Meibomian gland dysfunction or dry eye symptoms?

Cohen's Kappa Value: 0.96

Appendix B: *Condensed Downs and Black checklist results used to check the quality of the studies included in the analysis.*

		Reporting	External Validity	Bias	Confounding	Power	
Study	Year	Items 1-10	Items 11-13	Items 14-20	Items 21-26	Item 27*	Total/28
Intense Pulsed Light Applied Directly on Eyelids Combined with Meibomian Gland Expression to Treat Meibomian Gland Dysfunction. Rong, Tang, Tu, et al.	2018	6	3	4	4	1	18
Intense pulsed light treatment and meibomian gland expression for moderate to advanced meibomian gland dysfunction. Albietz and Schmid.	2018	7	3	5	3	1	19
Intense Pulsed Light Treatment for Dry Eye Disease Due to Meibomian Gland Dysfunction; A 3-Year Retrospective Study. Toyos, McGill, and Briscoe.	2015	9	3	5	3	1	21
Intense Pulsed Light Treatment for Meibomian Gland Dysfunction in Skin Types III/IV. Li, Lin, and Cheng.	2019	8	3	4	3	1	19
Intense regulated pulse light for the meibomian gland dysfunction. Karaca, Kemer, and Ozek.	2018	8	3	5	3	1	20
Long-Term Effects of Intense Pulsed Light Combined with Meibomian Gland Expression in the Treatment of Meibomian Gland Dysfunction. Rong, Tang, Liu, et al.	2018	7	3	4	6	1	21
Long-term effects of intense pulsed light treatment on the ocular surface in patients with rosacea-associated meibomian gland dysfunction. Seo, Kang, Ha, et al.	2018	8	3	5	3	1	21
Prospective Trial of Intense Pulsed Light for the Treatment of Meibomian Gland Dysfunction. Craig, Chen and Turnbull.	2014	7	3	4	4	1	19

In our modified Downs and Blacks checklist, item 27 was only worth 1 point. The question used in place for item 27 was: 27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes were calculated to detect a difference of x% and y%.

Appendix C: *Baseline characteristics of the studies included in the analysis.*

Study Information and Baseline Characteristics – IPL Therapy in MGD

Study	Year	Study Design	Study Location	N	Age (Mean)	Visual Acuity (Mean)	Misc.	Main Outcome To Be Measured	Number of IPL Treatments Administered
Intense Pulsed Light Applied Directly on Eyelids Combined with Meibomian Gland Expression to Treat Meibomian Gland Dysfunction. Rong, Tang, Tu, et al.	2018	Prospective, randomized, double-masked, controlled study	Beijing, China	44 Patients	N/A	logMAR BCVA: 0.12±0.26 (Intervention) 0.11±0.15 (Control)	Fitzpatrick 1/2/3/4: 0/16/15/14	MGYSS, SPEED Score, TBUT, CFS Score, Meibography findings	3 treatments at an interval of 4 week
Intense pulsed light treatment and meibomian gland expression for moderate to advanced meibomian gland dysfunction. Albietz and Schmid.	2018	Open-label prospective study	Queensland, Australia	26 patients (52 eyes)	54.7±15.6	N/A	Fitzpatrick 1/2/3/4 Skin Types: 3/17/1/5	OSDI, OCI, Schirmer test, TBUT, tear osmolarity, InflammaDry, central corneal sensation, conjunctival bulbar and limbal redness, eyelid margin redness, ocular surface fluorescein staining, meibum quality	3 treatments at baseline, 2 weeks and 6 weeks
Intense Pulsed Light Treatment for Dry Eye Disease Due to Meibomian Gland Dysfunction; A 3-Year Retrospective Study. Toyos, McGill, and Briscoe.	2015	Retrospective noncomparative interventional case series	United States of America	91 patients (182 eyes)	N/A Ranged from 21 – 84, Median: 54	N/A	Patients must be Fitzpatrick type 1, 2 or 3. Some type 4s accepted	TBUT,	4 treatments at an interval of 30 days
Intense Pulsed Light Treatment for Meibomian Gland Dysfunction in Skin Types III/IV. Li, Lin, and Cheng.	2019	Clinical Trial	Hong Kong	40 patients (80 eyes)	N/A 2 groups of patients: Group A < 40 years Group B > 40 years	N/A	12.5% FP type 3, 87.5% FP type 4	OSDI, TBUT, patient satisfaction, adverse events	3 treatments at an interval of 2 weeks between the first and secondtreatments, and at an interval of 1 month between the second and third treatments
Intense regulated pulse light for the meibomian gland dysfunction. Karaca, Kemer, and Ozek.	2018	Clinical Trial	Cankaya, Turkey	26 patients (52 eyes)	51.6±13	N/A	N/A	OSDI, TBUT, Schirmer test, Oxford grading, lid margin abnormality score, secretion quality and expressibility	3 treatments at an interval of day 1, day 15 and day 45
Long-Term Effects of Intense Pulsed Light Combined with Meibomian Gland Expression in the Treatment of Meibomian Gland Dysfunction. Rong, Tang, Liu, et al.	2018	Prospective, randomized, double-masked, controlled study	Beijing, China	28 patients (28 eyes)	42.17±17.62	N/A	FP 1/2/3/4: 0/8/18/2	MGYSS, TBUT	3 treatments with an interval of 4 weeks
Long-term effects of intense pulsed light treatment on the ocular surface in patients with rosacea-associated meibomian gland dysfunction. Seo, Kang, Ha, et al.	2018	Prospective study	Incheon, South Korea	17 patients (34 eyes)	64 (range 57-68)	N/A	N/A	OSCI, TBUT, staining score, NIKBUT, Miebomian gland parameters (lid margin vascularity, meibum expressibility and quality)	4 treatments at an interval of 4 weeks
Prospective Trial of Intense Pulsed Light for the Treatment of Meibomian Gland Dysfunction. Craig, Chen and Turnbull.	2014	Prospective, double-masked, paired-eye, placebo-controlled study	Auckland, New Zealand	28 patients, 28 eyes	45±15	N/A	N/A	NIBUT, SPEED score, lipid layer grade, tear evaporation rate (TER), tear meniscus height (TMH)	3 treatments at an interval of day 1, day 15 and day 45

Figure 1: *PRISMA flow diagram showing the screening process (including title, abstract and full-text screening).*

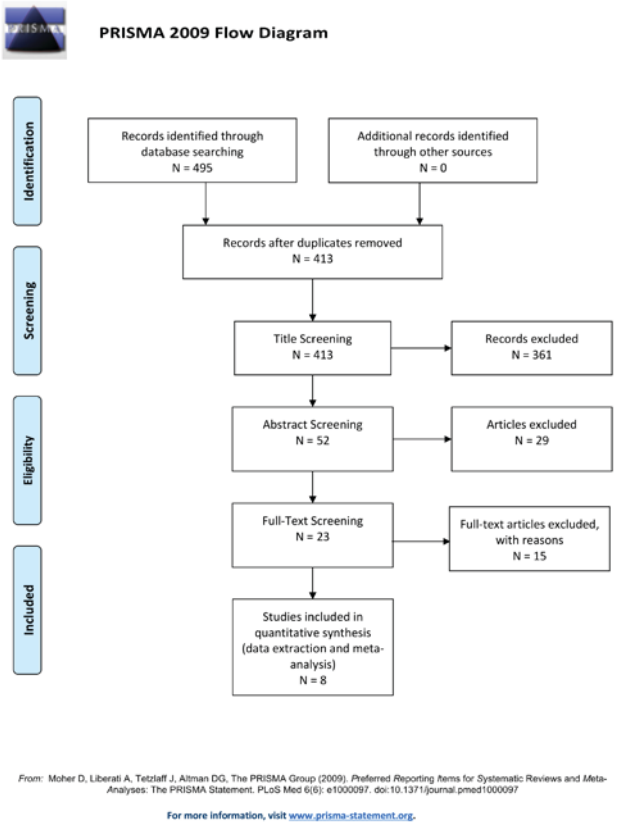


Figure 2: *Forest plot demonstrating the changes in TBUT values at various follow-up periods, including "less than 1 month", "1.5 - 2 months", "3 months", "6 months", and "12 months".*

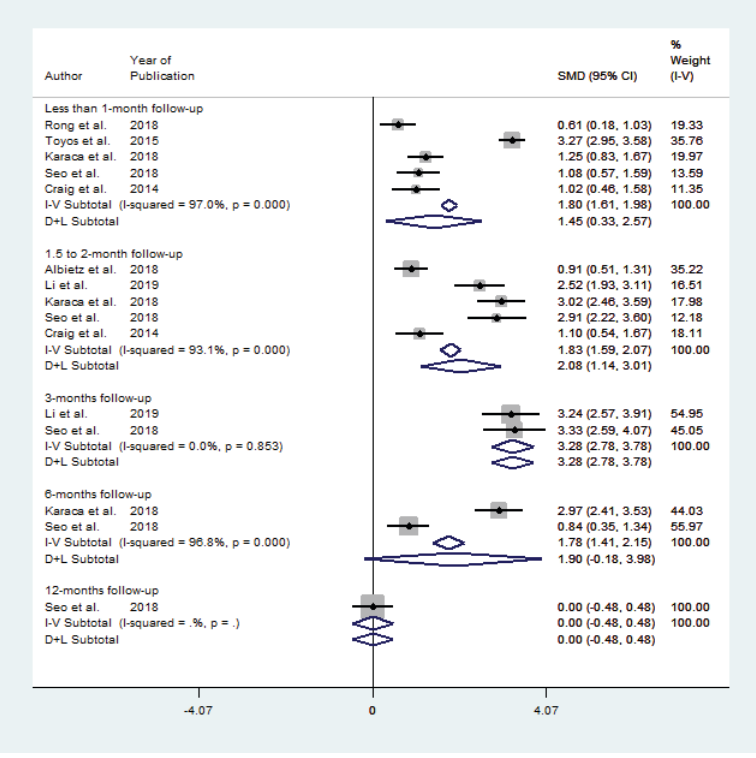


Figure 3: *Forest plot demonstrating the changes in Schirmer test values at various follow-up periods, including "less than 1 month", "1.5 - 2 months", and "6 months".*

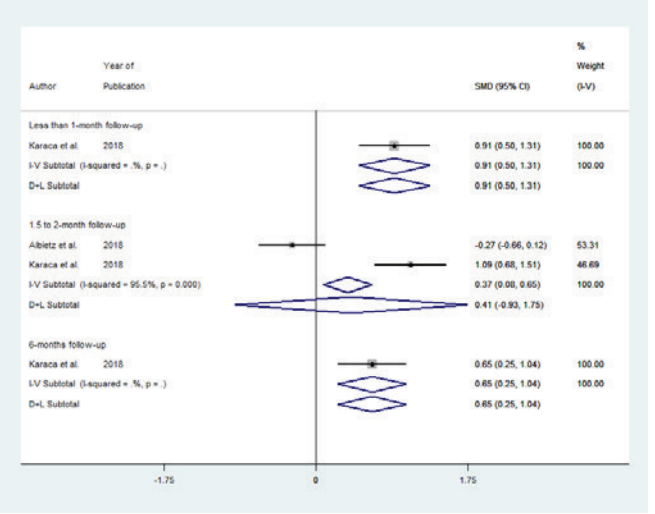


Figure 4: *Funnel plot for evaluating potential publication bias in studies assessing TBUT values.*

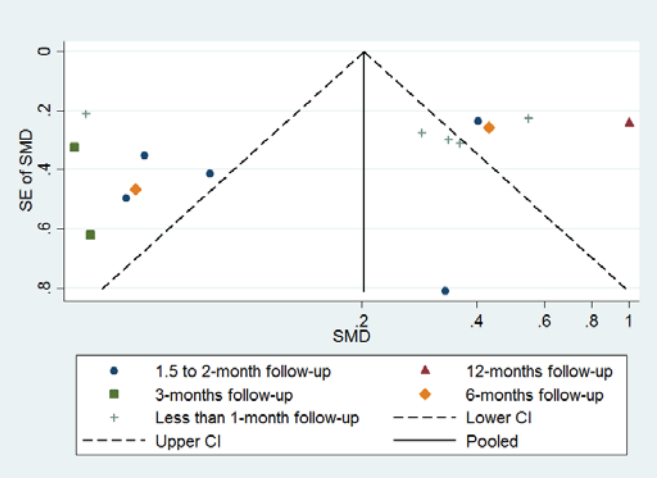
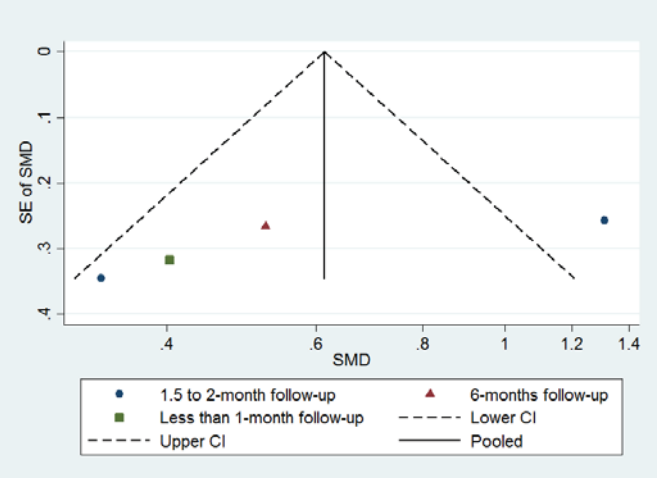


Figure 5: *Funnel plot for evaluating potential publication bias in studies assessing Schirmer test values.*



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