Intense pulsed light therapy (IPL) in the treatment of Meibomian gland dysfunction (MGD)

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Short Title: IPL in treatment of refractory MGD

Abstract:

Purpose: This was a prospective study to evaluate the efficacy and safety of Intense pulsed light therapy (IPL) using (E-Eye; E-SWIN, Paris, France) in meibomian gland dysfunction (MGD).

Patients and methods: The study included 46 adult patients ≥18 years with uncontrolled MGD [symptoms of dry eye disease (DED), Ocular Surface Disease Index score (OSDI) ≥13, and slit-lamp evidence of MGD]. Symptoms evaluation using OSDI, conjunctival injection, lower tear meniscus height (TMH), tear break-up time (TBUT), corneal staining, lid margin, and meibomian gland assessments, noncontact Sirius meibography were evaluated before treatment and 4 weeks after the final session of treatment. The changes in the best corrected visual acuity (BCVA) and intraocular pressure (IOP) were also reported to evaluate the safety of the procedure.

Results: There was a significant improvement in symptoms based on OSDI changes ($p<0.001$), a significant decrease in conjunctival injection, and a significant increase in TBUT from 3.8+1.1 seconds to 6.5+1.08 seconds. The Oxford corneal staining scale reduced significantly after IPL ($p<0.001$). TMH did not show a statistical improvement at the end of follow-up period ($p=0.2$). Compared to baseline, posterior lid margin rounding, irregularity, and vascularity were significantly improved after the treatments, while anterior blepharitis did not show a statistically significant change. Both meibomian gland secretion quality and expressibility showed a significant improvement at the end of follow-up period ($p<0.001$). Sirius meibography results after IPL showed a significant improvement in both meiboscore and MG loss in both upper lid (UL) and lower lid (LL) ($p<0.001$). There were no signs of skin blistering, swelling, redness, or depigmentation.

Conclusion: Intense pulsed light (IPL) using (E-Eye, E-Swin) is a safe and potentially effective treatment option in alleviating symptoms and signs of MGD.

Keywords: MGD, IPL, dry eye, Ocular Surface.

INTRODUCTION:

Meibomian gland dysfunction (MGD) is considered to be the major cause of dry eye disease (DED) mainly the evaporative component[1]. The incidence of MGD varies from 3.5% to as high as 70% depending on the geographical region; being more in Asiatic compared to western countries[2-3]. The characteristic feature of this chronic disease is terminal duct obstruction and/or qualitative/quantitative changes in the glands secretions; leading to compromised tear lipids and increased tear evaporation[4-5]. MGD results in tear film alteration, irritation and inflammatory symptoms, and ocular surface disease[6].

The current treatment paradigm of MGD includes warm compress application, lid hygiene, artificial tears (preservative-free), topical steroids, omega-3 fatty acids dietary supplementation, azithromycin antibiotics (topical and oral),

topical cyclosporine, and meibomian gland expression (MGX). Despite these varied treatment options, some patients are still resistant to therapy and do not experience a long-term relief because of poor compliance to therapies that limit their application in addition to being time-consuming, and some can be uncomfortable[7-9].

Intense pulsed light (IPL) therapy had been first applied in dermatology to treat various conditions. It is based on the delivery of intense pulses of non-coherent light with wavelengths of 500 to 1200 nm which targets numerous chromophores (such as melanin and hemoglobin). IPL was initially used in dry eye disease (DED) after improvement of dry eye symptoms in a patient with rosacea who received IPL therapy[2,10]. In 2017, IPL was listed as one of the physical therapies for dry eye in a report from the TFOS DEWS II (Tear Film and Ocular Surface Society International Dry Eye Workshop II)[11]. The aim of this study was to evaluate the effectiveness and safety of IPL (E-Eye; E-SWIN, France) in MGD patients.

PATIENTS AND METHODS:

This was a prospective interventional clinical trial that involved single group with no masking. Patients were recruited from the Ophthalmology outpatient department, DarAlShifa hospital Hospital, Kuwait between December 2020 and December 2021. The study was conducted according to the Declaration of Helsinki principles, was approved by the local Human Research, and Ethics Committee and was registered: www.clinicaltrials.gov/ct2/show//NCT04904874

Before enrolment, an informed written consent form was obtained from all participants after explanation of the nature of the procedure.

The inclusion and exclusion criteria:

The inclusion criteria were adult patients ≥ 18 years with MGD that was diagnosed based on: symptoms of dry eye disease, Ocular Surface Disease Index score (OSDI) ≥13, [12] and the evidence of MGD on slit-lamp examination which included: diffuse terminal duct obstruction, lid margin changes: hyperemia, thickening, irregularity and telangiectasia with quantitative and/or qualitative changes in meibomian glands secretion. [13-14] The followings were excluded: punctal occlusion; eyelid position; closure and blinking anomalies; active allergy or infection or inflammatory disease of the ocular surface unrelated to dry eye or MGD; contact lens wear; history of ocular surgery or trauma. Patients using systemic medications which alter the tear film; having systemic diseases affecting the ocular surface; patients with pigmented lesions in the treatment area; tattoos; or having skin treatments within 2 months; candidates with very dark or black African skin (Fitzpatrick Skin Type VI) were also excluded. Pregnancy and nursing mothers were not included.

Clinical Evaluation:

Subjects were evaluated before the IPL treatment and four weeks after the final session in order to assess the cumulative treatment effect. The subjective and objective assessments included the following: symptoms evaluation, conjunctival injection, corneal staining, tear meniscus height (TMH), tear break-up time (TBUT), lid margin changes and meibomian gland assessments (including secretion quality and expressibility of the meibomian gland). Noncontact meibography was used for non-invasive evaluation of the changes of meibomian glands morphology and quantification of meibomian gland loss (MGL). Best corrected visual acuity (BCVA) and intraocular pressure (IOP) changes were also documented for safety assessment.

- Symptom Evaluation: Patients' symptoms were evaluated using Ocular Surface Disease Index (OSDI)[16]. It contains 12 items with a scoring of 0 (no symptoms) to 100 (severe symptoms). The formula used for evaluation is: OSDI=D x 25/E, D represented the scores sum for all answered questions and E is the number of the answered questions. A final score of 0 to 12 means no disability, 13 to 22 means mild symptoms, 23 to 32 means moderate symptoms, and 33 to 100 means severe symptoms.

- Conjunctival injection: The slit lamp microscope was used to evaluate the conjunctival bulbar injection using Institute for Eye Research (IER) Grading Scale[17]. Score (0) represented grade 1 and score (3) represented grade 4 = severe bulbar conjunctiva redness.

- TMH: TMH in the central lower lids was measured using the slit lamp microscope (with a graticule in 0.05mm units). The average value of three readings was recorded[18].

- TBUT: The patient was asked to blink without squeezing for three to five times after instillation of 2% sodium fluorescein onto the bulbar conjunctiva. Then the patient stare without blinking under the cobalt blue light and the time between the last blink and the first dry spot appearance was recorded. The average value of three readings was reported[19].

- Corneal Staining: The corneal staining was divided into 6 groups using The Oxford corneal grading scale: (0) implies no staining and (5) implies severe staining[20].

- Eyelid Margin assessment: This included: rounding of posterior margin, irregularity/ notching, vascularity/ telangiectasia of lid margin, anterior blepharitis, and trichiasis. Each sign scored 0 = no/normal or 1= yes/abnormal. This was done according to the International Workshop on Meibomian Gland Dysfunction[13].

- Meibomian Gland Assessments: The quality of meibomian gland secretion was divided into four degrees: (0) = clear; (1) = cloudy; (2) = granular; (3) = toothpaste, while the expressibility of the meibomian gland was graded as follows: (1) = with light pressure; (2) = with moderate pressure; (3) = with heavy pressure[13].

- Noncontact meibography: A modified Sirius® Scheimpflug Camera (C.S.O, Costruzione Strumenti Oftalmici, Italy; bon OpticVertriebsgmbH, Lübeck, Germany) with Meibography Imaging software module was used. Following eversion of upper and lower eyelids, the meibomian glands were tracked in a trapezoidal area. The MG loss was defined as the percentage of the area without visible glands out of the total visible tarsal area. The grades of MG loss (Meiboscore) in each eyelid were scored as follows: grade 0 (no meibomian glands loss), grade 1 (the lost area was < 25% of the total area of meibomian glands), grade 2 (the lost area was 26% - 50% of the total area of meibomian glands), grade 3 (the lost area was 51% - 75% of the total area of meibomian glands), and grade 4 (the lost area was > 75% of the total area of meibomian glands).

- Safety Evaluation: The following were assessed on every visit, BCVA, intraocular pressure (IOP) using a noncontact tonometer (Canon TX-20, Japan). Inspection of the skin around the eyes for redness, blistering, swelling, depigmentation, or hair loss at the brow and forehead was also performed.

Treatment Procedure:

All subjects received three treatment sessions according to the following schedule: days (D) 1, D15, and D45 using the E-Eye machine provided by E-Swin company, France. IPL was applied to the skin area below the lower eyelids with intensity that ranged from 9.8 J/cm2 to 13.0 J/cm2. The intensity of energy was inversely related to the Fitzpatrick Skin Phototype Grading[15]. The globes were first protected with opaque metal goggles. In order to conduct the light and provide some degree of protection though an even spread of the energy, a 5.0 mm thick layer of ultrasound conductive gel was applied on the patient's face from tragus to tragus including the nose. For each eye, four overlapping flashes were applied to the skin below the lower eyelid. All the treatments were performed by a trained clinician. Post-treatment instructions included continuation of warm compresses with eyelid massage daily in addition to preservative free lubricants as required. Patients were also instructed to avoid the heat, exposure to the sunlight, and mechanical or chemical irritation of the treatment area within the first 24 hours after treatment.

Statistical Analysis:

The Statistical Package of Social Science (SPSS; Chicago, USA, version 25) was used for data analysis. The normality of data was tested with the Shapiro-Wilk test. Continuous variables were represented in mean ±SD for parametric variables and median (range) for non-parametric variables. The Paired *t*-test was used to compare parametric data while the Wilcoxon Signed-Rank test was used to compare non-parametric ones. Number and percent and were used to represent the categorical variables and were compared using the Chi-square test. The Mc Nemar test was used for binomial variables analysis.

RESULTS:

This study included 46 symptomatic participants with a mean age of 51.3 ± 6.8 years (range 40 to 62 years) with the clinical diagnosis of dry eye due MGD. The study included 16 males (34.8%) and 30 females (65.2%). One eye from each patient was included, the one with more severe symptoms or higher Meiboscore. The changes in both subjective and objective parameters of MGD patients after treatment series of IPL were illustrated in Table (1). Based on OSDI changes, there was a significant improvement in subjective symptoms ($p<0.001$). Regarding objective assessments, conjunctival injection decreased significantly and the TBUT increased significantly from an average of 3.8+1.1seconds to 6.5+1.08 seconds. The Oxford corneal staining scale reduced significantly after IPL ($p<0.001$). However, TMH did not show a statistical improvement at the end of follow-up period ($p =0.2$).

The meibomian gland secretion quality and expressibility showed a significant improvement at the end of follow-up period ($p<0.001$). Figure (1) showed the grading of both meibum quality and expressibility of the meibomian gland before and after IPL treatment.

Table (1): Subjective and objective assessments of MGD patients before (baseline) and after treatment series of intense pulsed light (IPL).

Measurement (scale)	Baseline evaluation	Post-treatment evaluation	P value
OSDI score (0 to 100)	25.9 ± 3.05 (20-32)	22.9 ±2.07 (19-27)	<0.001
Conjunctival injection (0 to 3)	1.0± 0.8 (0-3)	0.5±0.6 (0-2)	<0.001
TMH (mm)	0.14±0.06 (0.05-0.2)	0.14±0.05 (0.05-0.2)	0.2
TBUT (seconds)	3.8±1.1 (2-6)	6.5±1.08 (5-8)	0.03
Corneal staining (0-5)	1.26±0.9 (0-3)	0.72±0.72 (0-3)	<0.001
Meibomian gland quality (0-3)	1.96±6.9 (1-3)	0.91±0.62 (0-2)	<0.001
Meibum secretion expressibility (1-3)	2.02+0.49 (1-3)	1.33+0.47 (1-2)	<0.001

OSDI= Ocular Surface Disease Index, TMH= tear meniscus height, TBUT= tear break-up time.

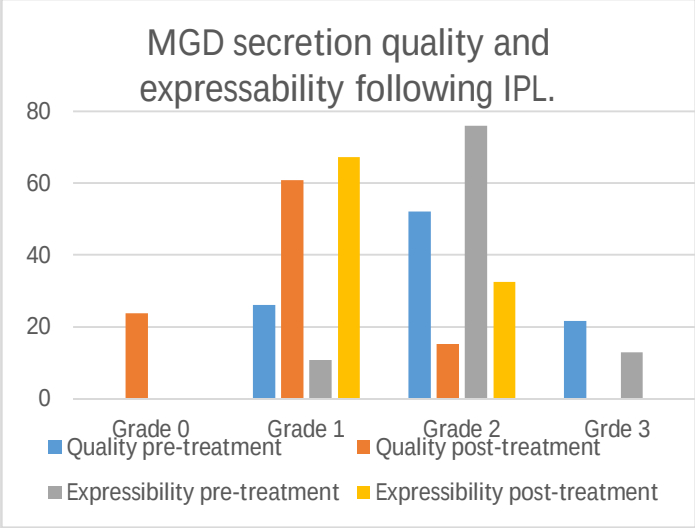


Figure (1): The grading of meibum quality and expressibility of the meibomian gland before and after IPL treatment.

Table (2) presented the eyelid margin assessment using five signs: rounding of posterior margin, irregularity, vascularity, trichiasis, and anterior blepharitis. All these signs except anterior blepharitis were improved significantly after the treatments ($p =0.25$).

Table (2): Eyelid margin signs evaluation before and after treatment series of intense pulsed light (IPL).

Parameter	Baseline evaluation	Post-treatment evaluation	P value
Rounding of posterior margin	37 (80.4%)	16 (34.8%)	< 0.001
Irregularity	36 (78.3%)	20 (43.5%)	< 0.001
Telangiectasia	38 (82.6%)	22(47.8%)	< 0.001
Trichiasis	0	0	-----
Anterior blepharitis	9 (19.6%)	6 (13%)	0.25

Mc Nemar test.

Sirius meibography results after IPL were shown in Table (3). Statistically significant differences were observed in both meiboscore and MG loss in both upper lid (UL) and lower lid (LL) ($p<0.001$). Figures (2) and (3) demonstrated the grading of Meiboscore in both UL and LL before and after IPL while

Figures (4) and (5) showed Sirius meibography of the lower lid of the same patient before and after IPL treatment.

Table (3): Meibogarphy results before and after intense pulsed light therapy (IPL).

Parameter (scale)	Baseline evaluation	Post-treatment evaluation	P value
Meiboscore UL (0-4)	1.63±0.74 (1-3)	1.2±0.7 (0-3)	< 0.001
Meiboscore LL (0-4)	1.43±0.6 (1-3)	0.87±0.5 (0-2)	< 0.001
MG Loss UL (%)	34.48±20.7 (13-74)	26.22±17.9 (8-73)	< 0.001
MG Loss LL (%)	28.39±15.2 (13-72)	20.11±11.7 (7-53)	< 0.001

Wilcoxon signed-rank test. UL: upper lid, LL: lower lid.

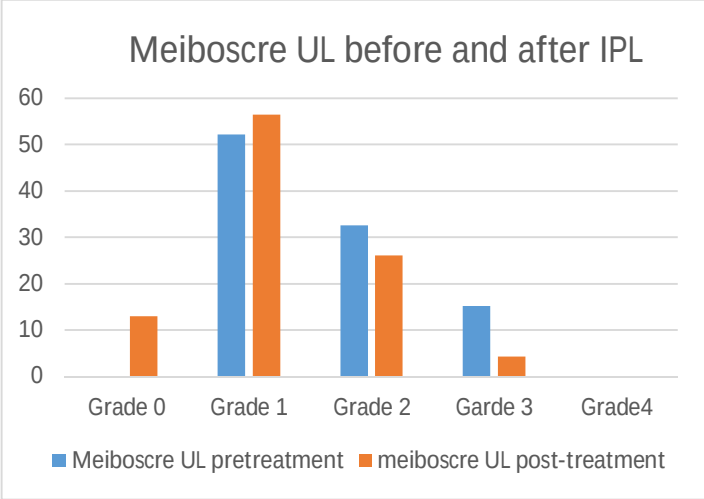


Figure (2): The grading of Meiboscore in UL before and after IPL.

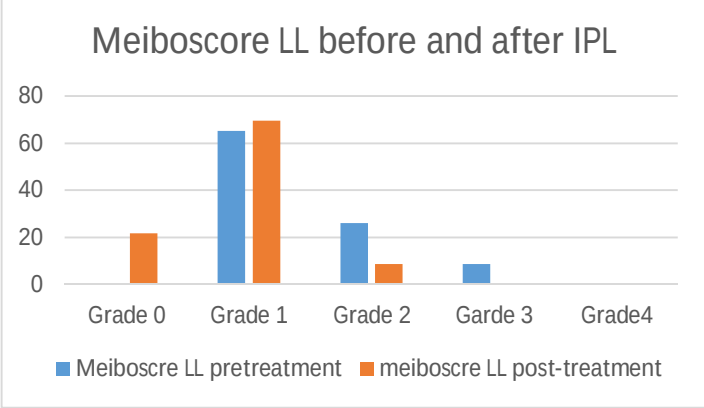
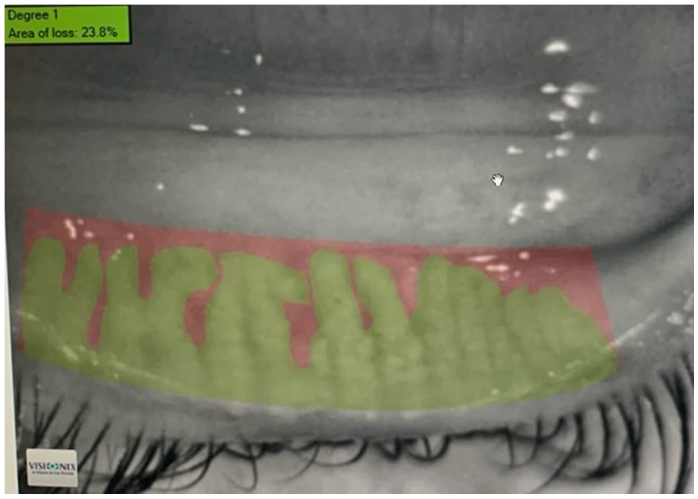


Figure (3): The grading of Meiboscore in LL before and after IPL.

Figures (4): Sirius meibography of the lower lid before IPL treatment.



Figures (5): Sirius meibography of the lower lid of the same patient after IPL treatment.

Regarding safety, BCVA and IOP showed no statistically significant changes at the end of follow up period. No signs of skin blistering, swelling, redness, or depigmentation. No hair loss at the brow and the forehead was observed.

DISCUSSION:

MGD is known to be one of the most common diseases encountered by ophthalmologists and is considered the most common cause of evaporative DED. The pathogenesis of MGD and DED was described as two vicious cycles linked by inflammation[21]. MGD is initiated as a result of various factors (skin disorders such as rosacea, eyelid inflammation, and microbial infections), resulting in an increase in the melting temperature of the meibum and blockage of glands orifices.

This leads to inflammation and atrophy of the meibomian glands. With the resultant tear film instability and corneal exposure, the DED vicious cycle is triggered and the ocular surface inflammation extends to the lid margins which feeds back into the MGD cycle[22].

IPL had proved its efficacy in treating patients with MGD, however, the mechanism of action is still unknown. Different potential mechanisms were proposed including abnormal blood vessels thrombosis, thermal heating of the glands causing meibum liquefaction, reduction of the turnover of epithelial cells thus decreasing the gland obstruction risk, activating fibroblasts and enhancing collagen synthesis; and decreasing lid marginal bacteria and eradicating Demodex[5,15,23,24,25].

Whatever its mechanism of action, our results proved the efficacy and safety of IPL (E-Eye; E-Swin) in treating patients with MGD. In our series, IPL treatment leads to a significant improvement in symptoms based on OSDI changes ($p<0.001$), a significant reduction in conjunctival injection and a significant increase in TBUT from 3.8±1.1 seconds to 6.5±1.08 seconds. The Oxford corneal staining scale reduced significantly after IPL ($p<0.001$). However, TMH did not show a statistical improvement at the end of follow-up period ($p=0.2$). Regarding eyelid margin signs when compared to baseline, rounding of posterior lid margin, vascularity and irregularity showed a significant improvement after the treatments, while anterior blepharitis did not show statistical improvement. Both meibomian gland secretion quality and expressibility showed a significant improvement at the end of follow-up period ($p<0.001$). Sirius meibography results after IPL showed a statistically significant improvement in both meiboscore and MG loss in both upper lid (UL) and lower lid (LL) ($p<0.001$). IPL proved to be a safe procedure proved by the absence of changes in BCVA or IOP. No signs of skin blistering, swelling, redness, or depigmentation.

Comparing our results to other studies might be limited by many factors: the different study designs, the MGD diagnostic criteria and severity, ethnicity and skin type, the investigated parameters, the IPL device used, number (4 or 5) and the intensity of flashes used per treatment, number of treatments (3 or 4) in addition to the length of follow-up period. Despite these factors, our results go more or less in agreement with the previous reports. In a double-masked, paired-eye, prospective controlled study, Craig JP et al[15] assessed 28 participants who underwent IPL treatment (E-Eye, E-Swin) to one eye and placebo treatment to the control eye at 1, 15, and 45 days. Subjective symptoms score using visual analogue scales (VAS), noninvasive tear break-up time (NIBUT), TMH, Lipid layer grade (LLG), and tear evaporation rate (TER) were compared between baseline and control values.

Lipid layer and NIBUT grade improved in the treated eye, however, TER and TMH showed no improvement. Symptoms scores improved in the treated eye with 86% of patients noting reduced symptoms. Karaca EE et al[26] evaluated 26 patients who underwent IPL with the same device used in our study but with five light pulses that delivered to one eye at the same regimen. Schirmer test and TBUT improved significantly on Day 45 (8.53 ± 4.31 mm vs 12.6 ± 3.14 mm and 4.53 ± 1.33 seconds vs 11.07 ± 2.87 seconds). Standard patient evaluation of eye dryness scores (SPEED) and OSDI improved ($p < 0.05$). There were no ocular side effects. Oxford grading, secretion quality and expressibility, and lid margin abnormalities showed no significant changes.

Gedar Totuk ÖM et al[27] retrospectively evaluated the same IPL device. Ten weeks after the treatment, there was **a** significant improvement in OSDI and meibography. Ocular surface staining scores was reduced, however, there was an increase in NIBUT and TMH by 47.34% and 22.16%, respectively. There were no side effects. Jiang X et al[28] also evaluated the safety and efficacy of E-Eye; E-Swin in MGD. Their results showed significant improvements in all the following: ocular surface symptoms (subjective face score), conjunctival injection, TBUT, eyelid margin signs, meibomian gland expressibility and secretion quality.

Albietz JM et al[29] found a significant improvement at week 8 following IPL (E-Eye; E-Swin) combined with expression of meibomian glands regarding the following parameters: gland expressibility, meibum quality, TBUT, lid margin, corneal staining, and conjunctival redness. However, symptom survey

outcomes, Schirmer I test, tear osmolarity, eyelid margin bacteria colony counts, and corneal sensitivity were unchanged. The reduction in the elevated Matrix metalloproteinases (MMPs) levels in the tears supports the theory that IPL treatment acts by decreasing inflammation. The obliterated vessels cannot continue to send pro-inflammatory mediators to the meibomian glands which affects the gland's function, destabilize both the tear film and the ocular surface[29].

Our study has its limitations. The study did not include a placebo control group, however, we found it difficult to have a control group with MGD that attended to receive a "mock" IPL treatment with no potential benefit. Another limitation is the short follow-up period. Further studies with longer follow-up periods, analysis of tear film layers, and antibacterial effects of IPL are needed to evaluate the long-term efficacy and mechanism of action of IPL.

In conclusion, Intense pulsed light (IPL) using (E-Eye, E-Swin) is a safe and potentially effective treatment option in alleviating MGD symptoms and signs. The development of evidence-based clinical guidelines and digging deep into the underlying mechanisms require further research to evaluate the maintenance of IPL treatment effect.

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DATA AVAILABILITY

All data are included in this article.

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Magda Torky. the author have no conflict of interest that are directly relevant to the content of this review.

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