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Effects of contact and non-contact laser photocoagulation therapy on ocular surface in patients with proliferative diabetic retinopathy

***Abstract*—**The aim of the study is to evaluate the effects of contact and non-contact laser photocoagulation (LP) on ocular surface changes and Ocular Surface Disease Index (OSDI) score in patients with proliferative diabetic retinopathy (PDR). This was a single center, prospective, randomised, parallel-controlled trial of pilot study in Hospital Universiti Sains Malaysia between June 2013 and May 2014. Eye with PDR was selected and randomised into 2 groups (Contact LP group and Non-contact LP group) by using random sampling envelope method. Contact LP group was treated with contact LP via slit lamp laser delivery system. Non-contact LP group was treated with non-contact LP via binocular laser indirect ophthalmoscopy system. Main outcome measures were Schirmer test value, tear film break-up time (TBUT) and OSDI score at baseline and at 3 months post laser therapy. Statistical analyses were performed using SPSS version 22.0. A total of 60 eyes were recruited (30 eyes in Contact LP and 30 eyes in Non-contact LP). Contact LP showed significant reduction of TBUT ($p = 0.038$) and significant increase in mean OSDI score ($p = 0.001$) at 3 months post laser therapy. However, there was no significant difference of mean change of Schirmer test value and TBUT between the two groups except for OSDI score ($p = 0.044$). Both mode of laser deliveries (contact LP and non-contact LP) showed comparable effects on ocular surface disease in PDR patient that underwent laser pan retinal photocoagulation.

***Keywords* — Laser photocoagulation, proliferative diabetic retinopathy, ocular surface disease**

1 INTRODUCTION

Diabetic retinopathy is a chronic and potentially sight-threatening disease. It is the major cause of blindness in persons above 40 years of age in a newly industrialized country [1]. Several studies [2, 3] have shown that dry eye syndrome is more common among diabetic patients. One study has shown that the degree of keratoepitheliopathy was severe, tear film break-up time (TBUT) and tear secretion were significantly reduced in the diabetic patients [4].

Laser photocoagulation (LP) has become a valuable modality to treat diabetic retinopathy. The most common method of laser delivery is via slit-lamp, which is the contact LP. Whereas in the non-contact LP, laser is delivered through a binocular indirect ophthalmoscope. Binocular indirect ophthalmoscope laser delivery system is an acceptable modality used worldwide in ophthalmology for selected patient with proliferative diabetic retinopathy (PDR). However, there is limited evidence base study or clinical trial.

Binocular indirect laser photocoagulator was newly designed to enable visualisation of the entire fundus during laser procedure [5]. The delivery system of the laser beam provides the clinician with a better view of the whole fundus than the standard slit-lamp delivery system, and become the ideal method for pan retinal photocoagulation in the treatment of diabetic retinopathy [5,6], central retinal vein obstruction [5] and barrier laser for retinal tears [5,7-10].

Indirect photocoagulation delivery system can be applied freely and in any direction under an overall view of the fundus. This considerably reduces the time required for treatment. Mizuno et al reported that the time required for diffuse photocoagulation with 1000 spots was accomplished within 15 minutes, while the slit-lamp system required more than 30 minutes to obtain the same amount of laser spots [5].

Law and Fan documented that their initial experience using laser indirect ophthalmoscope was not only successfull in the treatment of patients with diabetic retinopathy but also in patient with venous occlusions, peripheral retinal holes and in post-vitrectomy cases [11]. The efficacy of indirect or non-contact LP for the treatment of PDR demonstrated that more than

80% of diabetic patients having stable or improved vision post treatment [12]. Ambresin *et al.* reported that among patients with high risk PDR previously treated with slit-lamp pan retinal photocoagulation, 58.8% achieved quiescent PDR with fill-in indirect argon laser [13].

Indirect ophthalmoscope delivery system for LP is the method of choice for patient with difficulty to sit at slit-lamp or eye with poor media such as vitreous haemorrhage, lens opacity, poorly dilated pupil or in children [11,14,15].

LP is one of the risk factors for ocular surface disease in diabetic retinopathy [16]. Pardos & Krachmer reported that there was a statistically significant change in endothelial cell density in the six-week follow-up post laser therapy [17]. In contact LP, direct contact of the laser contact lens and coupling fluid onto the ocular surface can cause direct trauma to the cornea, and this is made worse by friction during manipulation of the laser contact lens [18]. On the other hand, while delivering non-contact LP, the eye is kept opened by a speculum and this could expose the cornea and lead to excessive dryness of the ocular surface.

The objective of this study is to evaluate the effects of contact and non-contact LP on ocular surface changes and Ocular Surface Disease Index (OSDI) score in patients with PDR that underwent laser pan retinal photocoagulation.

2 METHODS

This is a pilot study of a single center, prospective, randomised, parallel-controlled trial. It was conducted at Hospital Universiti Sains Malaysia between June 2013 and May 2014.

The study adhered to the Tenets of the Declaration of Helsinki and the study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia {Ref. no: USMKK/PPP/JEPeM [263.3.(6)]}. Written informed consent was obtained from all patients before conducting the study. This study was retrospectively registered with Trial Registration: ISRCTN Registry: ISRCTN12055187.

2.1 Subjects

All diabetic patients aged between 25 to 70 years old with newly diagnosed PDR who attended Hospital Universiti Sains Malaysia between June 2013 and May 2014 were included in this study. Any PDR patients who were on regular eye drops or wearing contact lens or PDR patients with poor media that obscured view of delivering laser therapy to the retina were excluded from this study. None of the PDR patients had previous history of intraocular surgery or ocular trauma including chemical, thermal or radiation injuries. PDR patients with neovascular glaucoma were also excluded.

Sixty eyes were identified and randomised into two groups (30 eyes for each group), the Contact LP group and Non-contact LP group by using random sampling envelope method. A stack of opaque envelopes were prepared with half of the envelopes containing a piece of paper with the word “CONTACT LP” and the remaining halves stated “NON-CONTACT LP”. These envelopes were shuffled and stored at the randomisation room. One identified medical assistant drew the envelope for each eye. Principle investigator that performed the eye assessments was blinded to the group allocation. Identified ophthalmologist that performed the laser therapy was masked to eye’s clinical parameters.

2.2 Baseline Measurement

All eligible patients had their history taken and had slit lamp examination done. The eyes were dilated with gutt tropicamide 1% eyedrops for fundus examination. Baseline parameters of Schirmer test value, TBUT and OSDI score were measured. The eye assessment was performed by principle investigator and was blinded to the group allocation.

The Schirmer test was done with topical anaesthesia (gutt proparacaine hydrochloride 0.5%) in a confined room with the fan off and patient seated upright. One drop of topical anesthesia was applied into conjunctival sac and excess tears were wiped away gently. It was performed with standardised strip of Schirmer filter paper. The patient was asked to look up and the lower eyelid was gently pulled laterally and inferiorly. The filter paper was placed in the lateral canthus away from the cornea and left in place for 5 minutes with the eyes open. After 5 minutes, the Schirmer paper was removed and reading was taken according to the amount of wetting on the calibrated scale printed on the Schirmer paper.

TBUT was performed with moistened fluorescein strips being introduced to the conjunctival sac with minimal stimulation. The patient was then instructed to blink several times to ensure adequate and even mixing of fluorescein. TBUT was then assessed using slit lamp biomicroscope at 10 times magnification

using cobalt blue illumination. The patient was then asked to blink normally and once the last blinking stopped, the stopwatch was started. The interval between the last complete blink and the first appearance of a dry spot in the stained tear film was measured. This test was repeated 3 times for each eye and the mean was calculated and taken for each eye separately.

The Ocular Surface Disease Index (OSDI; Allergan Inc, Irvine, California) was used to evaluate the ocular disease symptoms. OSDI is a questionnaire consisting of 12 questions with scoring from 0 to 4: 0, none of the time; 1, some of the time; 2: half of the time; 3: most of the time; and 4, all the time. Patient was asked regarding visual function, ocular symptoms and environmental triggers for the past one week. The OSDI was assessed on a scale of 0 to 100, with higher scores representing greater disability.

2.3 Laser photocoagulation therapy

After obtaining the baseline parameters, the eligible eyes were randomised into 2 groups of laser therapy by using random sampling envelope technique. Contact LP group was treated with contact LP via slit lamp laser delivery system. Non-contact LP group was treated with non-contact LP via binocular laser indirect ophthalmoscopy system. LP was delivered at week 1, week 2 and week 3, with total laser shots of 3000-5000 shots by one identified ophthalmologist and was masked to eye's clinical parameters.

In Contact LP group, a single drop of gutt proparacaine hydrochloride 0.5% was instilled into patient's eye for anesthesia before the placement of the applanation contact lens. A coupling fluid (occ Carbomer 0.22% and Hypromellose 0.3%) and contact lens were used for contact LP. Contact lenses that are used are Mainster Wide Field contact lens and Goldmanns three-mirror contact lens. Patient was seated at Argon laser slit lamp machine. The settings of the laser were as follow: spot size of 200 microns; power of laser 150 mw and titrated accordingly to achieve light intensity burns and exposure time of 0.1 seconds.

Whereas in Non-contact LP group, LP was delivered to retina via binocular indirect laser delivery system. Patient's eye received a single drop of gutt proparacaine hydrochloride 0.5% topical anesthesia solution before the procedure. Patient was asked to lie down on a treatment couch in supine position and an eye speculum inserted gently without touching the cornea. Gutt artificial tears without preservative were instilled intermittently by a trained assistant to keep the ocular surface moist. A non-contact 20 diopter condensing lens was used to visualize and to aim the laser beam onto the retina. The settings of the laser were as follows: power of laser 150 mw and titrated accordingly to achieve light intensity burns and exposure time of 0.1 seconds.

2.4 Measurement post laser therapy

The patient with the eye that completed 3 sessions of laser therapy was followed-up at 3 months post intervention and was seen again by the same principle investigator. Schirmer test, TBUT and OSDI questionnaire were repeated in the similar fashion at 3 months post intervention of laser therapy for both groups.

2.5 Statistical analysis

Statistical Package for Social Sciences (SPSS) software version 22.0 was used for statistical analysis. In descriptive analysis the mean values and standard deviation (SD) were used. All values were tested for normality (using histogram graphical test and Kolmogorov-Smirnov test) and noted normally distributed. Pre and post laser therapy mean Schirmer test value, TBUT and OSDI score for each group were tested by using paired t-test. Independent t-test was then used to compare the difference of mean change of Schirmer test value, TBUT and OSDI score between the two groups. P values of <0.05 were taken as significant data.

3 RESULTS

A total of 60 eyes, which underwent either contact LP (30 eyes) or non-contact LP (30 eyes) were evaluated. The mean age of patient in Contact LP group was 51.0 (SD 10.4) years and 55.1 (SD 8.2) years in Non-contact LP group ($p = 0.207$). All patients recruited in this study were Malays.

At 3 months post laser, the mean Schirmer test value had reduced from baseline in both groups. Although both groups showed reduction of TBUT at 3 months post laser, only Contact LP group demonstrated significant reduction ($p = 0.038$). There was also significant increase in mean OSDI score at 3 months post laser in Contact LP group ($p=0.001$) (Table 1).

In terms of mean change (Table 2), the difference of mean change between pre and post laser therapy of Schirmer test value, TBUT and OSDI score were greater in Contact LP group compared to Non-contact LP group. However, only the mean change of OSDI score showed

significant difference (p=0.044) between the two groups.

There was no reported complications related to the laser therapy performed such as corneal burn, iritis, inadvertent lasering of fovea or retinal vessels in both Contact LP and Non-contact LP groups.

Table 1. Comparison of mean Schirmer test value, TBUT and OSDI score at baseline and 3 months post laser for each group.

	Baseline Mean (SD)	3 Months Post Laser Mean (SD)	Mean Difference (95% CI)	P value
Contact LP				
Schirmer test value (mm)	8.7 (4.0)	7.7 (3.5)	-0.93 (-2.21, 0.35)	0.148
TBUT (second)	8.1 (2.2)	7.2 (2.0)	-0.90 (-1.75, -0.05)	0.038
OSDI score	20.7 (12.6)	24.4 (13.0)	3.76 (1.75, 5.77)	0.001
Non-contact LP				
Schirmer test value (mm)	7.8 (3.6)	7.5 (2.8)	-0.30 (-0.99, 0.39)	0.379
TBUT (second)	8.2 (2.7)	7.7 (2.2)	-0.53 (-1.11, 0.05)	0.069
OSDI score	27.0 (18.5)	27.9 (19.3)	0.92 (-1.12, 2.97)	0.353

Paired t-test, p value <0.05 significant
Abbreviation: LP, laser photocoagulation; TBUT, tear film break-up time; OSDI, Ocular Surface Disease Index.

Table 2. Comparison of mean change of Schirmer test value, TBUT and OSDI score between the two groups.

	Mean Change Mean (SD)	Mean Difference (95% CI)	t-statistic (df)	P value
Schirmer test value (mm)				
Contact LP	-0.93 (3.44)	-0.63 (-2.06, 0.79)	-0.888 (58)	0.378
Non-contact LP	-0.30 (1.84)			
TBUT (second)				
Contact LP	-0.90 (2.26)	-0.30 (-1.30, 0.70)	-0.60 (58)	0.549
Non-contact LP	-0.60 (1.52)			
OSDI score				
Contact LP	3.76 (3.91)	2.83 (0.08, 5.59)	2.09 (32)	0.044
Non-contact LP	0.92 (3.98)			

Independent t-test, p value <0.05 significant
Abbreviation: LP, laser photocoagulation; TBUT, tear film break-up time; OSDI, Ocular Surface Disease Index.

4 DISCUSSION

Diabetic patients are at higher risk of developing ocular surface disease as well as diabetic keratopathy. Laser therapy is one of the risk factors for ocular surface disease in diabetic patient with retinopathy [16]. In this study, our objective was to evaluate the effects of contact and non-contact LP therapy on ocular surface changes and OSDI score in patients with PDR.

The PDR patients in our study had the baseline mean Schirmer test measurement in both groups at less than 10 mm. Degree of keratopathy in diabetic patients is correlated with the severity of diabetic retinopathy [19,20]. We compared the Schirmer test value between baseline and at 3 months post laser treatment in Contact LP and Non-contact LP groups. We observed that there were reduction of the mean Schirmer test values at 3 months post treatment in both groups and Contact LP showed a greater reduction. However, there was no significant difference of mean Schirmer test values between baseline and at 3 months post laser in each group. Decreased tear production was thought to be a result of neuropathy involving the innervation of lacrimal gland [21,22].

Total and reflex tear production in diabetes using Schirmer test without anesthesia were significantly reduced, but the basal secretion remained unchanged [23,24]. On the other hand, other studies reported a reduction in basal tear secretion [16,21]. We adopted the Schirmer test with anesthesia in order to measure the basal tear secretion. Schirmer test with topical anesthesia is more objective and reliable than that without anesthesia in reflecting the status of dry eye [25] and increasing the sensitivity of the study [26].

Both the Schirmer test and baseline TBUT showed reduction in PDR patients three months post laser. TBUT is a test for tear film stability. Unstable tear film is a common finding in patients with reduced aqueous tear production or increase tear evaporation. Lower TBUT has been identified in poorer diabetic control patients [21]. It is also reduced in patients with advanced diabetic retinopathy stage [4]. In our study, we observed that the baseline means TBUT for both groups was less than 10 seconds. This finding is consistent with other studies carried out to assess the ocular surface disorder in diabetes mellitus patients. TBUT in diabetic patients are significantly lower than normal population [16].

We compared TBUT between baseline and 3 months post laser treatment in Contact LP and also in Non-contact LP group. There was significant reduction of TBUT in contact LP group at 3 months post treatment (p=0.038) but not in Non-contact LP group (p=0.069). From these results, PDR eyes that underwent contact LP demonstrated a decrease in TBUT at 3 months post treatment. This could be explained by the usage of viscous coupling fluid for the laser contact lens and friction between the diseased corneal epithelium and the coupling fluid. Dogru *et al* concluded that the use of viscous coupling agents during contact LP may be detrimental for corneal epithelium in diabetic retinopathy patients [18]. It is suggested to popularize the use of

indirect ophthalmoscope laser delivery system and use of less viscous coupling agents for contact laser in order to reduce the effects of contact laser towards ocular surface [27].

Comparing the results of mean change between pre and post laser therapy in Schirmer test and TBUT between Contact LP and Non-contact LP group, there was no significant difference for Schirmer test (p=0.378) and TBUT (p=0.549). This shows that the effect of contact laser on ocular surface is comparable to that of non-contact LP. Both methods of delivering laser to retina produce changes and reduction in Schirmer test and TBUT.

In the present study, OSDI questionnaire is adopted to evaluate the symptoms of ocular surface disease. It comprises of 12-item questionnaire to assess the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning. We noted that our patients had reported having at least mild dry eye at base line.

We also compared the OSDI score in both groups at 3 months post laser. Contact LP group showed significant increase of the OSDI score (p=0.001) at 3 months post laser. There was also increase OSDI scoring in Non-contact LP group at 3 months post laser but it was not significant (p=0.353). We found that there was significant difference of mean change of OSDI score between the two groups (p=0.044). OSDI questionnaire is a subjective self-reporting assessment, in which patient is able to relate their personal experience when answering the questionnaire. Our postulation is that contact LP with the direct application of laser contact lens onto patient's ocular surface might create discomfort and thus resulting in increasing in OSDI score, indicating worsening of ocular symptoms. Non-contact LP is thought to be more comfortable and less stressful conducted in a reclining position. In addition, it required shorter time of treatment, thus patients preferred non-contact laser over slit lamp contact laser [5,12].

We were unable to compare our findings to other studies because, to our knowledge there is no study comparing the ocular surface disease between contact LP and non-contact LP.

Other clinical assessments that are frequently used in assessing ocular surface disease in diabetic eyes include procedures such as corneal and conjunctival staining, impression cytology of the conjunctival epithelium, tear osmolarity and corneal sensitivity measurement. Based on these various assessment tools, the cornea of diabetics is abnormal compared to normal population [21-23, 28-33].

In this study, there are several limitations. Ocular surface changes in diabetes mellitus can be reflected in many other tests such as corneal sensitivity, corneal fluorescein staining, Rose Bengal staining, tear osmolarity test and conjunctival impression cytology which we did not investigate on. OSDI questionnaire is initially designed to assess dry eyes. Poor visual acuity in PDR can affect the interpretation of vision-related function in OSDI. The poor visual acuity could be related to the retinopathy per se and may not reflect the true ocular surface disease symptoms. Another limitation in this study is the glycated haemoglobin (HbA1c), which is the biomarker for diabetic control was not assessed among the PDR patients. Poor diabetic control might demonstrate more severe effects on ocular surface.

Beside diabetic control, duration of performing the laser procedure also might contribute to the effects on ocular surface. However, in this study, we did not assess the duration of performing the laser. We recommended that in future studies, HbA1c and duration of performing the laser should be included beside other tests for ocular surface changes.

5 CONCLUSION

Both mode of laser delivery (contact LP and non-contact LP) showed comparable effects on ocular surface disease in PDR patient that underwent laser pan retinal photocoagulation. Future research with larger sample size is warranted to establish the absolute effect of laser therapy towards ocular surface.

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