Transscleral vs transpupillary diode laser photocoagulation for the treatment of zone II type 1 retinopathy of prematurity: Anatomical and refractive outcomes

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Purpose: To compare the anatomical and refractive outcomes of transscleral diode versus transpupillary laser photocoagulation for the treatment of zone II type 1 retinopathy of prematurity (ROP). **Methods:** In this prospective comparative interventional case series, infants with type 1 ROP in zone II were assigned to either transpupillary or transscleral laser based on the surgeons' expertise area. The rate of regression, need for retreatment, and structural and biometric outcomes at month 6 were evaluated and compared between the two treatment groups. **Results:** In total, 209 eyes were enrolled; 145 eyes of 77 infants and 64 eyes of 33 infants and were in transscleral and transpupillary groups, respectively. There was no significant difference in baseline characteristics between the groups. There was no significant difference in retreatment rates (1.6% vs. 3.4%; *P* = 0.669) and progression to stage 4 (1.6% vs. 2.8%; *P* = 0.999) between the transpupillary and transscleral groups, respectively. At month 6, the mean spherical equivalent was 0.31 ± 3.57 and 0.44 ± 2.85 diopters, and the axial length was 18.28 ± 6.22 and 18.36 ± 6.87 mm in the transpupillary and transscleral groups, respectively, without a significant difference between groups. There was no significant difference in the rate of myopia (43.8% vs. 33.8%; *P* = 0.169) and high myopia (4.7% vs. 4.8%; *P* = 0.965) in transpupillary and transscleral groups at month 6. **Conclusion:** The transpupillary and transscleral laser photocoagulation routes are both effective in the treatment of zone II type 1 ROP and show no significant differences in anatomical or refractive outcomes in relation to the route chosen.

Key words: Refractive error, retinopathy of prematurity, transpupillary laser photocoagulation, transscleral laser photocoagulation

Retinopathy of prematurity (ROP) is characterized by incomplete growth of the retinal vessels and compensatory formation of new vessels at the border of avascular retina, which can lead to macular dragging and retinal detachment.[1] The incidence of visual impairment related to this condition is highest in developing countries.[2] Adherence to standard guidelines for screening, which may be different for every country, is crucial for lowering the incidence.[2,3]

Despite recent investigations introducing various anti-VEGFs in the management of ROP, laser photocoagulation remains the standard of care, especially in zone II ROP.[4] Laser can be applied to the retina via two routes: transpupillary and transscleral. There are pros and cons to each route. Although transpupillary laser is the most common and regarded as the standard treatment option, cataract formation is a concern with this route of treatment.[5,6] The possible necessity for conjunctival incision and general anesthesia prevent transscleral route from becoming popular among surgeons.[7,8] However, Parvaresh *et al*.[8] employed transscleral laser under topical anesthesia without conjunctival incision and showed favorable outcomes in threshold and type 1 ROP.[9]

As previous studies were mostly limited to small case series or evaluated threshold disease, in this study, we aimed to analyze the outcomes of zone II type 1 ROP treated with transscleral versus transpupillary laser photocoagulation.

Methods

This prospective interventional comparative case series was conducted from January 2017 to November 2018 at Farabi eye hospital ROP center. Patients with zone II type 1 ROP (i.e. Zone II, stage 2 or 3 with plus disease in at least one eye) were enrolled in this study.[10] As the transscleral laser treatment

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could not be applied to zone I, patients with zone I ROP who needed treatment were excluded. The study adhered to the tenets of the Declaration of the Helsinki and was approved by the institutional review board committee of the affiliated university. Written informed consent was obtained from all participants' parents prior to enrollment in the study.

Patients were assigned nonrandomly to two laser treatment arms, transpupillary [Fig. 1a] and transscleral [Fig. 1b], based on the surgeons' preference and experience. Lasers were performed by three surgeons (MI, AF, and RR). All the infants referred for treatment to MI were lasered via transscleral route and all referred to AF or RR were treated via transpupillary route. Both eyes were treated in the same session and with the same method of treatment, if needed.

The procedures were performed in the operating room under either sedation or general anesthesia, with cardiac and respiratory monitoring by an expert anesthesiologist. Infrared diode (810 nm) laser was applied to avascular retina anterior to the ridge. Laser parameters selected at the beginning included a starting power of 350 mW and a duration of 300 ms. These parameters were then adjusted to achieve a creamy-colored feature of laser spots one-third of laser spot diameter apart. The diode laser instrument (Iridex, Oculight SLx, Trimode-810 nm, USA) was employed and relevant probes were used for transpupillary or transscleral method of laser application through a dilated pupil.

In the transscleral technique, an application probe is used that functions as a scleral indenter.

All patients were visited weekly to monitor treatment responses; if any large skipped area persisted in the presence of a nonregressed neovascular tissue at one-month post-laser, retreatment would be scheduled within one week [Fig. 1].

Gestational age (GA), birth weight (BW), sex, postmenstrual age at first exam and at the time of treatment, and zone and stage of ROP were recorded for each patient. All patients were followed for a period of six months. Primary outcome was defined as the rate of regression of new vessel and plus. Secondary outcomes included refractive error and axial length at the final six months follow-up, as well as the rate of unfavorable outcomes and complications such as macular folds or dragging, or progression to ROP stage 4 or 5 in each treatment arm.

Cyclorefraction was performed at baseline, one, three, and six-months post treatment. Myopia and high myopia were defined as a spherical equivalent (SE) ≤ −0.25 diopters (D) and SE ≤ −5 D, respectively. Axial length was measured six months after laser treatment using an A-scan biometer (Carl Zeiss Meditec, Germany).

We performed a student t-test or Mann–Whitney U test to compare the continuous variables, and a Chi-square test to analyze the categorical characteristics between the two groups. Binary logistic regression was used to evaluate the potential factors affecting myopia. Statistical analysis was performed using SPSS software version 16.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

In total, 209 eyes were recruited in the study; 64 eyes of 33 infants were assigned to the transpupillary laser treatment arm, and 145 eyes of 77 patients were assigned
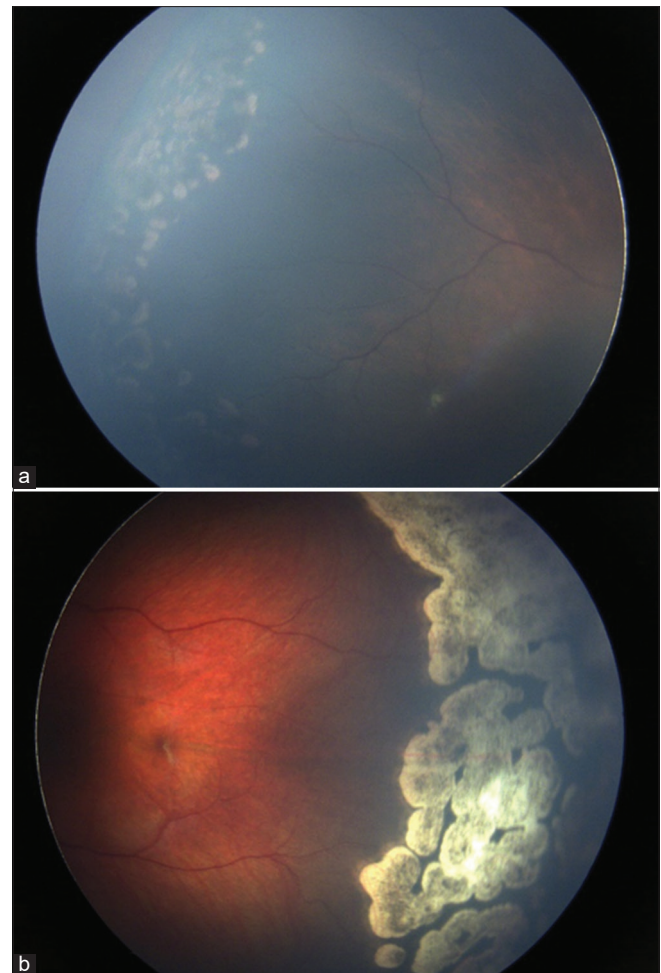

Figure 1: Fundus photograph showing laser spots applied via the (a) transpupillary and (b) transscleral routes

to the transscleral laser treatment arm. Mean GA in the transpupillary and transscleral groups was 28.9 ± 2.1 and 28.8 ± 2.0 weeks ($P = 0.719$), respectively. Both eyes were treated in 93.9% of patients in the transpupillary group and in 88.3% in the transscleral group ($P = 0.358$). Demographic and baseline clinical characteristics were not significantly different between the two groups [Table 1].

The average duration of each session was 40 min for the transpupillary route and 30 min for the transscleral route. The average number of spots was 998 (range: 670–1500) for transpupillary and 629 (400–1150) for transscleral route.

Six eyes required additional laser treatment: one (1.6%) in the transpupillary laser and five (3.4%) in the transscleral laser group ($P = 0.669$) [Table 2]. The average interval between the initial session and additional sessions of laser treatment was 4.8 ± 1.6 and 11 weeks in transpupillary and transscleral groups, respectively. Five eyes progressed to stage 4: one (1.6%) in the transpupillary group and four (2.8%) in the transscleral group ($P = 0.999$); no eyes developed a macular fold or dragging.

At the time of the first screening examination, the mean sphere was 1.33 ± 2.42 and 1.24 ± 1.92 D, cylinder was − 0.37 ± 0.96 and − 0.32 ± 0.52 D, and SE was 1.15 ± 2.5

Table 1: Comparison of baseline demographic characteristics between study groups

Variables	Transpupillary laser (64 eyes from 33 patients)	Transscleral laser (145 eyes from 77 patients)	P*
Sex (Male)	37 (57.8%)	73 (50.3%)	0.319
Bilateral	31 (93.9%)	68 (88.3%)	0.358
Gestational age (weeks)	28.9±2.1	28.8±2.0	0.719
Birth weight (gr)	1230.6±335.5	1220.3±362.7	0.847
Postmenstrual age at first exam (weeks)	33.4±3.5	33.8±3.1	0.332
Postmenstrual age at treatment (weeks)	34.5±4.1	34.6±3.6	0.217
Stage			
2	12 (18.8%)	28 (19.3%)	0.924
3	52 (81.3%)	117 (80.7%)	

*Based on Student's *t*-test or Chi-square test.

and 1.08 ± 1.93 D in transpupillary and transscleral groups, respectively (*P* > 0.05 for all comparisons). The SE trends during 6 months of follow-up are shown in Table 3. Baseline hyperopia increased and peaked at month one. A subsequent decline in hyperopia was then observed in both groups to the final follow-up at month six.

At month 6, there was no significant difference in sphere, cylinder, or SE between study groups [Table 3]. Final SE was 0.31 ± 3.57 D in transpupillary group and 0.44 ± 2.85 D in transscleral group (*P* = 0.594). Mean ALs at month 6 were also similar in the transpupillary (18.28 ± 6.22) and transscleral groups (18.36 ± 6.87; *P* = 0.733). Prevalence of myopia in the transpupillary group (43.8%) and the transscleral group (33.8%) was similar at month 6 (*P* = 0.169). There was no significant difference in the prevalence of high myopia between transpupillary and transscleral groups (4.7% vs. 4.8%; *P* = 0.965).

Potential factors affecting myopia at month 6 were evaluated in Table 4. GA was the only factor that correlated with myopia at month 6 (odds ratio = 0.737, 95% confidence interval: 0.635–0.856; *P* < 0.0001). There was no significant association between the route of laser delivery (transpupillary or transscleral), BW, treatment age, stage of ROP (stage 2 or 3), or myopia at month 6.

There were no serious anterior segment-related complications in either group. Mild vitreous hemorrhage was detected in four eyes (2.8%) in the transscleral group on the first post-operative day, all of which resolved spontaneously.

Discussion

Ablation of the avascular retina is the mainstay of the ROP treatment in its early stages.[4,10] Laser therapy destroys avascular retina and can be administered transsclerally or transpupillary. Transscleral laser generates larger areas of scarring compared to the transpupillary method but is still smaller than those produced by cryotherapy. Providing larger spots may decrease the time of laser procedure and anesthetic exposure. The size of the spots corresponds to the diameter of the transscleral probe, which is 1500 μM.

The transpupillary route is the preferred method by many surgeons, although concerns regarding cataract formation, iris atrophy, and hyphema exist.[5,6,11] In cases where a full mydriasis cannot be achieved, the transscleral method may be considered as the laser is applied on the retina via the sclera and not through the pupil.

Table 2: Comparison of anatomical outcomes between study groups

Variables	Transpupillary laser (*n*=64)	Transscleral laser (*n*=145)	P*
Additional laser treatment			
Stage 2	0	3 (2.1%)	
Stage 3	1 (1.6%)	2 (1.4%)	
Total	1 (1.6%)	5 (3.4%)	0.669
Progression to stage 4			
Stage 2	0	3 (2.1%)	
Stage 3	1 (1.6%)	1 (0.7%)	
Total	1 (1.6%)	4 (2.8%)	0.999

*Based on Chi-square test.

Table 3: Comparison of refractive and biometric outcomes at 6 month

Variables	Transpupillary laser	Transscleral laser	P*
Sphere (D)	0.80±3.51	0.87±2.81	0.808
Cylinder (D)	−0.98±0.76	−0.85±0.76	0.305
SE (D)	0.31±3.57	0.44±2.85	0.594
Axial length (mm)	18.28±6.22	18.36±6.87	0.733

*Based on Mann-Whitney U test

Table 4: Factors associated with presence of myopia at 6 months

Variables	Odds ratio (95% Confidence interval)	P*
Gestational age	0.737 (0.635-0.856)	<0.0001
Birth weight	0.999 (0.997-1.000)	0.134
Stage 3	0.551 (0.264-1.152)	0.113
Mode of treatment (Transpupillary laser)	1.665 (0.878-3.157)	0.118
Treatment age	0.975 (0.915-1.039)	0.431

*Based on binary logistic regression

This comparative case series revealed no significant difference in terms of rate of regression, side effects, or progression to more advanced stages of ROP between transscleral and transpupillary laser treatment groups during a six-month

follow-up period. A favorable outcome was achieved in more than 95% of eyes with either treatment modality. Seiberth *et al.* investigated infants with threshold ROP treated with these two routes of laser photocoagulation.[12] However, our study is the first one that compares the results of these two types of laser in the treatment of zone II ROP. Our anatomical results were comparable with the results of previous investigations using either transpupillary (success rate of 71%–100%)[12-15] or transscleral (success rate of 97.6% by Parvaresh *et al*.[8] and 96% by Seiberth *et al*.[16]) laser. However, some complications specific to transscleral laser were reported by Haller *et al*.[17]. They used this method for creating chorioretinal adhesion during retinal detachment surgery, scleral buckle. They observed complications such as small breaks in Buch's membrane, scleral thermal effect, and mild intraretinal and vitreous hemorrhages. In conclusion, they stated that transscleral laser is safe and effective and the incidence of minor complications decreases with increasing experience of the surgeon. Davis *et al*.,[7] however, demonstrated a lower rate of favorable outcomes (79%) of ROP for transscleral laser. That study, however, included a population with higher risk characteristics, such as lower GA and BW, and more advanced stages of ROP (threshold ROP) compared to our study.

Another reason for the noninferior results in the transscleral group compared with the transpupillary group in our study may be related to the highly experienced surgeon performing it. Although more complications have been reported for the transscleral method, such as Bruch's membrane rupture and intraocular hemorrhages, we have only observed a resolving vitreous hemorrhage in 2.8% of patients treated via the transscleral method. As zone II cases were selected for this study, the surgeon did not perform any conjunctival incision, solid edema; as such, conjunctival trauma was not a concern.

At 6 months, the prevalence of myopia and high myopia was not statistically significantly different between the two study groups. Several factors have been proposed to play a role in the development and progression of myopia in premature infants, including prematurity itself, presence and severity of ROP, and therapeutic interventions.[18-21] Two-year results of the BEAT-ROP study showed that infants that received laser have a statistically significant lower spherical equivalent and higher incidence of high myopia compared to those treated with intravitreal bevacizumab.[20] This may be due to an arrest in the development of the anterior segment, which can lead to a steep cornea, shallow anterior chamber, and thickened crystalline lens. It has been speculated that growth factors released from retinal tissues are essential for the development of the anterior segment.[18] Ablation of the peripheral retina by laser may disturb local signaling pathways, whereas intravitreal bevacizumab may be less destructive and allow for the growth of retinal vessels later in life.

No study in the literature has evaluated the refractive outcome of eyes with ROP treated with transscleral laser photocoagulation. The mean SE and prevalence of myopia at 6 months in our study are consistent with previous studies evaluating the refractive outcome of transpupillary laser with less than 1 year follow-up. Quinn *et al*.[22] reported a rate of 55%–61% for myopia and 17%–20% for high myopia at 6 months. Halan *et al*.[23] reported a similar rate: 62.5% for myopia and 18.8% for high myopia at 12 months. It should

be noted that the duration of follow-up and the inclusion of exclusively zone II ROP eyes in our study may have affected the interpretation of refractive results.

Another parameter evaluated in this study was the refractive change after laser treatment. Our study reveals a hyperopic shift in ROP treated eyes that peaks at month one and then gradually declines. This trend is similar to some previous reports recruiting premature eyes with or without ROP.[24,25] Early hyperopia could be attributed to rapid thinning of crystalline lens and decrease in the corneal curvature of premature eyes after birth.

In the present study, the incidence of myopia did not correlate with the severity (higher stage) of ROP. In the ETROP study, there was no significant difference in refractive outcome between early treated eyes with high-risk prethreshold and those eyes treated only if threshold ROP developed.[22] GA was the only factor found to have a negative correlation with myopia, which is in accordance with some other studies.[21,26] Other factors, including more posterior zone of involvement,[21] lower birth weight,[21,26] type of therapeutic interventions,[20] and more extensive laser treatment[27], have also been shown to affect refractive results.

Our study had several limitations: no blinding or randomization (which may have induced selection bias and surgeon factor), small sample size, and short-term follow-up. Additionally, as only infants with ROP in zone II were included in this study, the result of the study cannot be generalized to the other zones of disease. Also, the location of zone II (anterior, mid, or posterior) was not recorded.

Conclusion

In summary, we showed the efficacy and safety of the transscleral laser for treatment of zone II type 1 ROP and found it to be comparable to the outcomes attained by the transpupillary route of laser. Favorable anatomical outcome was achieved in more than 95% in each laser treatment group.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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