Original Article

Safety and efficacy of 532 nm frequency-doubled Nd-YAG green laser photocoagulation for treatment of retinopathy of prematurity

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Purpose: To evaluate the safety and efficacy of 532 nm frequency-doubled Nd-YAG green laser for treatment of retinopathy of prematurity (ROP). **Methods:** This retrospective interventional case series included infants undergoing treatment for ROP with 532 nm green laser between January 2012 and March 2017 at a single tertiary-care referral center. Review of clinical records was done to identify baseline ROP characteristics, procedural difficulties, complications related to the laser procedure and outcome of treatment at ≥ 1 year of follow-up. **Results:** There are about 347 eyes of 182 infants were included in this present study. ROP presented in zone I in 76 eyes (21.9%) and zone II in 271 eyes (78.1%). Tunica vasculosa lentis (TVL) was present in 43.8% and pre-existing vitreous hemorrhage in 4.6% of the eyes. 532 nm green laser could be performed as a primary procedure in all eyes, including those with TVL. 322 eyes completed a minimum follow up of 1 year with a mean follow up of 22.8 months (range, 12–54 months). At the last follow-up visit, 298 (92.5%) of the 322 eyes had a favorable outcome. On logistic regression analysis, pre-existing fibrovascular proliferation (p = 0.04) and new-onset fibrovascular proliferation after treatment (p = 0.001) were the most significant independent predictors of poor outcome. Complications encountered were new-onset hemorrhage in 36 eyes (11.2%), anterior segment ischemia in two eyes (0.006%) and cataract in one eye (0.003%). **Conclusion:** 532 nm frequency-doubled Nd-YAG green laser appears to be safe and effective in the treatment of ROP.

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Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the immature retina in infants with young gestational age and low birth weight.[1] It is the leading cause of preventable childhood blindness in the developing countries.[2-4] Cryotherapy was amongst the first widely accepted treatment strategies for the management of ROP.[5] This was followed by reports of laser treatment for ROP.[6-14] Not only is laser easier to administer, the final visual and structural outcomes have also shown to be better with laser as compared to cryotherapy.[6,7] Various types of laser have been reported for the treatment of ROP. Initially an argon green laser (488-528 nm) was used followed by diode laser (810 nm).[8,9] Results of the ETROP study established the efficacy of diode laser photocoagulation in early treatment of high-risk pre-threshold ROP. The study showed reduction in unfavorable visual outcomes from 19.8% to 14.3% and unfavorable structural outcomes from 15.6% to 9%.[10,11] Currently, diode laser is considered the standard of care for laser photocoagulation in ROP.[12-14]

For majority of the adult retinal vascular diseases a frequency doubled Nd: YAG green laser (532 nm) is most commonly used across the globe and is the only laser available.[15] However, there is paucity of data for use of 532 nm green laser for treatment of ROP.[16-19] The additional expense incurred in the purchase of a separate diode laser indirect ophthalmoscope (LIO) for ROP treatment may not be a viable option for many in the developing and underdeveloped countries. Moreover, premature babies with treatment requiring ROP may be few and not enough to justify acquiring a separate diode laser for this purpose. The major concerns with green laser for use in ROP have been the possibility of absorption of laser energy by tunica vasculosa lentis (TVL) leading to the formation of cataract and lack of penetration in the presence of vitreous hemorrhage. Cataract formation was reported to the tune of 1% to 6% with argon laser compared to 0.003% with diode laser.[11] Previous studies on green laser have either been with a small sample size[16,17,19] or not addressed these concerns directly.[18] Frequency-doubled 532 nm Nd: YAG green laser is being routinely used for the treatment of ROP at our center after the initial published reports.[16,17] The purpose of this study is to report the safety and efficacy of this laser for ROP treatment in a large cohort of preterm infants across the spectrum of the disease.

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Methods

This was a retrospective, non-comparative, interventional case series. The study was approved by the institute ethics committee and adhered to the tenets of the declaration of Helsinki. All infants who underwent treatment with 532 nm green laser indirect ophthalmoscope delivery system for ROP between January 2012 and March 2017 at a tertiary care institute were enrolled. A chart review of their clinical records was done to retrieve various parameters including demographics, risk factors for development of ROP (birth weight, period of gestation, in born/out born status, multiple pregnancies, oxygen exposure, respiratory distress syndrome, blood transfusion, neonatal jaundice, septicemia), type and zone of ROP, type of laser used, laser parameters, any procedural difficulties during laser, need for supplemental laser/surgery and final outcome with laser. Wide-field fundus images taken with the help of RetCam3 (Natus Medical Incorporated, Pleasanton, CA, USA) were reviewed for both pre and post laser features.

Treatable ROP was classified as either type 1 ROP, aggressive posterior retinopathy of prematurity (APROP), and hybrid ROP.[20,21] Type 1 ROP was defined as per the ETROP study and included one of the following: (1) Zone I, any stage ROP with plus disease (2) Zone I, stage 3 ROP with or without plus disease (3) Zone II, stage 2 or 3 ROP with plus disease.[10] APROP was defined as per the international classification of retinopathy of prematurity (ICROP) revisited classification as plus disease, flat neovascularization in zone 1 or posterior zone 2, intra-retinal shunting, hemorrhages and no clear demarcation between vascular and avascular retina.[20] Hybrid ROP was classified as per the study by Sanghi *et al.*[21] in eyes with presence of ridge tissue (characteristic of Type I ROP) along with flat neovascularization (characteristic of APROP) or matt-like proliferation in vascularized retina along with features of APROP in the same eye.

All eyes treated with 532 nm frequency-doubled Nd: YAG green laser (IRIS Medical Oculight TX, IRIDEX, CA, USA or Novus Spectra, Lumenis Ltd., Yokneam, Israel) were included in the study. Before laser treatment, the pupils were dilated with 1 drop of cyclopentolate 0.5%, tropicamide 0.4%, and phenylephrine hydrochloride 2.5% instilled into each eye twice, 15 minutes apart. Laser treatment was done under topical anesthesia (proparacaine hydrochloride 0.5%) after separating the lids with a speculum and under monitoring in a neonatal intensive care unit. Scleral depression was used for visualization of the periphery using a 20-diopter condensing lens. Power settings varied between 100 to 250 mW with an exposure duration of 100 ms to 200 ms. Laser parameters were titrated to achieve pale white burns in a confluent pattern (less than half burn width apart) to the avascular retina right up to the ora serrata.[22,23] Post treatment all eyes received betamethasone 0.1% and tobramycin 0.3% eye drops, four times a day for 1-2 weeks.

Intra and post treatment records were evaluated for any procedural complications and disease regression with or without sequelae. Development of cataract or posterior synechiae were looked for in each eye at every visit using the retro-illumination provided by direct visualization with an indirect ophthalmoscope and by moving closer to the eye using the magnification provided by the 20-diopter lens. Infants with incomplete documentation of records and post-laser follow-up of less than 1 year were excluded from the final outcome analysis. Outcome at last follow-up was defined as (A) Complete success if there was regression of disease with no sequelae, (B) Qualified success if there was regression of disease with sequelae (progression of fibrovascular proliferation (FVP), narrowing of arcades, disc/macular drag, extra-foveal stable tractional retinal detachment) or (C) Failure if there was progression to fovea involving tractional retinal detachment (TRD) or the need for surgery. Various factors including demographics, pre-existing risk factors, baseline clinical characteristics and post treatment clinical features were compared to the outcome to classify the risk factors for poor outcome. Student's t-test was used to compare independent linear variables and a Chi-square test for nominal variables. Logistic regression analysis was performed to analyze any factor adversely affecting the outcome. $P < 0.05$ was considered statistically significant.

Results

Three hundred and forty-seven eyes of 182 infants underwent treatment for ROP using 532 nm green laser during the study period. All these were treatment naïve eyes, with no laser or anti-vascular endothelial growth factor (anti-VEGF) injection treatment received beforehand. The mean birth weight of the infants was 1198.75 ± 318.49 grams (range 627 – 2500 grams) and mean gestational age was 28.84 ± 2.16 weeks (range 24 – 37 weeks). The mean post-menstrual age at laser treatment was 35.37 ± 3.16 weeks. One-hundred fifty-seven (86.3%) infants were out-born (referred to us from neonatal intensive care units elsewhere). The remaining 25 infants (13.7%) were in-born and managed in the neonatal intensive care unit of our institute.

At presentation, 135 (38.9%) eyes had Type I ROP, 147 (42.4%) had APROP and 65 (18.7%) eyes were diagnosed with hybrid ROP. Of the 347 eyes, zone I disease was seen in 76 eyes (21.9%). Of the 76 eyes, 11 eyes (3.2%) had posterior zone I disease, while 65 (18.7%) had vessels growing into anterior zone I. Majority of the laser treated eyes (271 eyes - 78.1%) had zone II ROP. All eyes had plus disease at the time of treatment. Tunica vasculosa lentis (TVL) was present in 141 eyes (40.6%), pre-existing FVP in 111 eyes (32%), pre-retinal hemorrhage in 128 eyes (36.9%) and vitreous hemorrhage in 16 eyes (4.6%). The risk factor and clinical profile of all infants is detailed in Table 1.

Laser treatment could be performed in all eyes irrespective of the presence or absence of TVL. Laser could be completed in both eyes, in a single sitting in all but one baby. Average number of laser spots applied were 3517 ± 1624 (range 975 – 5944 spots). No ocular complications such as corneal edema, hyphema, iris burns or vitreous hemorrhage were noted during the procedure in any of the eyes. Conjunctival chemosis causing difficulty in laser application was seen in 6 eyes. Systemic complications during the procedure included repeated desaturation/apnea in 11, persistent bradycardia in 2 and vomiting in 2 infants. Laser had to be abandoned or rescheduled in 3 babies due to these systemic complications. Only one of them required a second session of laser.

Of the 182 infants (347 eyes) included in the study, 168 infants (322 eyes) completed a minimum follow up of 1-year (mean follow up 22.8 months, range 12–54 months). Of these 322 eyes, 258 (80.13%) had complete success while 40 (12.42%) had a qualified success. In the forty eyes with

Table 1: Univariate analysis between various parameters and outcome after treatment of ROP with 532 nm Green Laser

	Complete Success* (*n*=258)	Qualified Success† (*n*=40)	Failure‡ (*n*=24)	*P*
Risk Factors				
Mean Birth Weight±SD (grams)	1207.8±337.5	1240.8±289.3	1196.6±219.6	0.814[a]
Mean Gestation±SD (weeks)	28.8±2.14	29.5±2.59	28.3±1.86	0.078[a]
Out born status	218	35	23	0.299[b]
Multiple births	79	12	5	0.605[b]
Ventilation	157	23	16	0.767[b]
Blood Transfusion	104	8	14	*0.007*[b]
Neonatal Jaundice	77	7	1	*0.010*[b]
Respiratory Distress Syndrome	90	11	11	0.328[b]
Septicemia	59	3	4	0.072[b]
Presenting features				
Diagnosis				0.570[b]
Type 1 ROP	103	15	8	
APROP	101	23	13	
Hybrid ROP	54	2	3	
Zone				*<0.001*[b]
Posterior Zone I	3	7	1	
Anterior Zone I	50	3	4	
Zone II	205	30	19	
TVL	102	21	18	*0.002*[b]
Pre-existing FVP	82	15	14	*0.030*[b]
Retinal Hemorrhage	100	17	11	0.740[b]
Vitreous Hemorrhage	8	6	2	*0.004*[b]
Post Treatment features				
Mean no. of laser spots	3421±1638	3576±1183	4261±2258	0.101[a]
New onset hemorrhage	18	12	6	*<0.001*[b]
New onset FVP	21	21	11	*<0.001*[b]
Supplemental Laser	20	10	8	*<0.001*[b]

ROP=Retinopathy of Prematurity, SD=Standard Deviation, APROP=Aggressive Posterior Retinopathy of Prematurity, TVL=Tunica Vasculosa Lentis, FVP=Fibro-Vascular Proliferation, *regression of ROP with no sequelae, †regression of ROP with sequelae (progression of FVP, narrowing of arcades, disc/macular drag, extra-foveal stable tractional retinal detachment), ‡progression to fovea involving tractional retinal detachment or the need for surgery, [a]Mann-Whitney U test, [b]Fisher exact test

qualified success, 15 had type I ROP, 23 had APROP while 2 eyes demonstrated features of hybrid ROP. There are about 15 eyes with qualified success (37.5%) had pre-existing FVP at the time of green laser treatment. About 9 of these 15 (60%) had extension of this FVP, leading to sequalae. Fresh onset FVP was seen in 21 eyes (52.5%). This led to narrowing of temporal vascular arcades in 19 eyes (47.5%) and extra-foveal stable TRD in 11 eyes (27.5%). Twenty-four eyes (7.45%) had an unfavorable outcome after green laser treatment. Of the 24 eyes with an unfavorable outcome, 5 (20.8%) progressed to stage 4A ROP with fovea-threatening TRD requiring lens sparing vitrectomy, 14 (58.3%) had stage 4B ROP and 3 (12.5%) had stage 5 ROP. About 3 of the eyes which developed stage 4B ROP underwent lens sparing vitrectomy while two underwent lensectomy with vitrectomy. None of the eyes that developed stage 5 ROP underwent any further intervention.

Cataract developed in only one of the 322 eyes (0.003%). Both eyes of an infant developed anterior segment ischemia after laser treatment. This baby presented at 18 days of life with a birth weight of 1650 grams and gestational age of 29 weeks. There was no TVL at presentation, but posterior segment showed avascular loops with flat NVE in zone II with plus disease. A diagnosis of APROP in zone II was made and the laser was done on the 19th day of life. The right eye received 3520 laser spots while the left eye had 1692 laser spots. The right eye developed anterior segment ischemia with cataract and subsequently went into phthisis bulbi. The left eye could be salvaged with intravitreal bevacizumab, topical corticosteroids and cycloplegic agents. Late development of cataract was not observed in any of the eyes after a minimal follow-up of 1 year. Thirty-six eyes developed new onset pre-retinal or vitreous hemorrhage after the laser, 23 of these eyes had APROP at presentation. Of these 36 eyes, only 6 had unfavorable structural outcome (progressed to stage 4B or 5) with all belonging to the APROP cohort. Six eyes (all APROP, 4 in Zone I) required anti vascular endothelial growth factor injection after the primary sitting of laser due to incomplete regression of the disease. About 3 of these eyes further had a sitting of supplemental laser after the injection. However, all these had a successful structural outcome following treatment.

In the eyes with zone I ROP, 53 of the 68 eyes had complete success (77.9%), while 10 (14.7%) had qualified success. There

are about 5 (7.4%) had an unfavorable structural outcome. These results were comparable with ROP presenting in zone II (p = 0.570). The presence of TVL did not hinder the laser treatment in any of the eyes. Despite small pupil in the beginning of treatment in eyes with severe TVL, all eyes had reasonable dilation to deliver adequate laser burns as the procedure progressed due to mechanical dilation of the pupil.[22] Of the 141 eyes with TVL, 102 (72.3%) had a complete success, 21 (14.9%) had qualified success and 18 (12.8%) had an unfavorable outcome. The chances of unfavorable outcome were significantly more as compared to the eyes without TVL (p = 0.002).

Univariate analysis was done to evaluate factors contributing to poor outcome [Table 1]. Infants with history of blood transfusion (p = 0.007) and neonatal jaundice requiring double volume exchange transfusion (p = 0.01) had significantly higher chances of an unfavorable outcome. Amongst the clinical features at presentation, ROP with TVL (p = 0.002), pre-existing FVP (p = 0.03) and vitreous hemorrhage (p = 0.004) had significantly higher adverse outcome. After green laser treatment, development of a fresh hemorrhage (p < 0.000) or FVP (p < 0.000) and the need for a supplemental laser (p < 0.000) were significantly associated with development of retinal detachment. On multivariate logistic regression with outcome as dependent variable, pre-existing FVP (p = 0.04, odd ratio = 6.43) and new onset FVP post treatment (p = 0.001, odds ratio = 28.9) were the most significant independent predictors of unfavorable outcome.

Discussion

Laser ablation of the avascular retina has been established as the treatment of choice for ROP.[6-14] Current evidence supports the use of diode laser for this purpose,[12-14] but 532 nm green laser is increasingly being used in developing countries. Various studies have reported favorable structural outcomes ranging from 71% to 97% with the use of diode laser.[11-12,24-27] Present study used 532 nm green laser in 322 eyes with minimum of 1-year follow-up. The overall favorable structural outcome in this study was 92.5% which is comparable to the large studies with 810 nm diode laser. Proportion of favorable outcome was slightly lower in our study as compared to the previous studies with green laser [Table 2]. This could be attributed to the higher number of APROP eyes in our study (42.6%). The study by Shi *et al*.[18] had 7% APROP eyes while the study by Chhabra *et al*.[19] had only 3.4% APROP eyes. Studies by Lira *et al*.[16] and Sanghi *et al*.[17] did not include any APROP eyes. APROP represents a more severe form of ROP and is known to be associated with poor outcomes despite confluent laser.[24-26] In our study, 90.5% of APROP eyes showed regression with 532 nm green laser treatment. This was lower than type 1 ROP (93.7%) and hybrid ROP (94.9%), though this difference was not statistically significant (p = 0.058).

The main concerns in treatment with green laser comes in eyes with severe disease and TVL. TVL is usually seen as a deterrent for 532 nm green laser treatment of ROP and laser induced cataracts are said to occur more in eyes with TVL.[9] It is hypothesized that this wavelength is absorbed by hemoglobin in blood, which can lead to localized burns in the area of TVL.[8] However, in our series TVL was present in 44% of the eyes and laser could be performed in all without any additional complications like hyphema or cataract. In the previous studies on green laser for ROP, only the study by Sanghi *et al*.[17] mentions about presence/absence of TVL. Even though that study reported no complication, it was limited by its small numbers and shorter follow up. The only large study by Shi *et al*.[18] does not address these concerns at all, and is mainly focused on the regression/progression of the disease.

Laser treatment of ROP has been associated with various complications which can be attributed directly to the effects of laser. These include corneal and iris burns, induction of cataract, anterior segment ischemia, bleeding into the anterior chamber and vitreous.[8-9,27-29] Vitreous hemorrhage has been reported with the use of green laser for ROP by Chhabra *et al*.[19] In our study, the laser related complications were anterior segment ischemia in both the eyes of an infant (0.006%), cataract in one eye of the same infant (0.003%) and new onset hemorrhage in 36 (11.2%) eyes. The incidence of cataract was much less than that reported with Argon laser (1 – 6%) and comparable to that reported with diode laser.[8,9] Anterior segment ischemia has been reported with argon green and diode laser.[30,31] However, this is the first report of anterior segment ischemia with frequency doubled Nd-YAG green laser. This particular infant (birth weight 1650 grams, gestational age 29 weeks) was treated on day 19 of life. Prematurity, early onset of disease and need for treatment at a small post-conceptional age could have contributed to the development of anterior segment ischemia in this child. Anti-vascular endothelial growth factors like bevacizumab have been previously described to help in the management of this complication.[32] this proved effective in salvaging one of this infant, while the other went into phthisis. New onset hemorrhage after laser treatment may not

Table 2: Comparison of studies using green laser (532 nm) for the treatment of ROP

Study	Year	Type of ROP[20,21]	No. of eyes	Eyes with APROP	Eyes with TVL	Complications	Favorable Outcome
Lira *et al*.[16]	2008	Threshold ROP	31	Nil	Not included	None	96.7%
Sanghi *et al*.[17]	2010	Type 1 ROP	100	Nil	20%	None	97%
Shi *et al*.[18]	2016	Type 1 ROP and APROP	312	7%	Not evaluated	None	93.9%
Chhabra *et al*.[19]	2018	Type 1 ROP and APROP	59	3.4%	Not evaluated	Mild vitreous hemorrhage - 5 eyes	93.2%
Present study	2019	Type 1 ROP, APROP and Hybrid ROP	322	42.6%	43.8%	New onset haemorrhage-36, Anterior segment ischemia-2 eyes, Cataract-1 eye	92.5%

ROP=Retinopathy of Prematurity, APROP=Aggressive Posterior Retinopathy of Prematurity, TVL=Tunica Vasculosa Lentis

be directly related to the laser treatment, since majority (23/36) of eyes with new onset hemorrhage had APROP and it could be related to disease severity. Alternatively, it can also occur in the natural course of the disease. In the eyes that developed this complication, only 50% had a complete success. This was a highly significant predictor of poor outcome ($p < 0.001$)

We found various factors such as history of blood transfusion, neonatal jaundice, ROP presenting with TVL/FVP/hemorrhage, post treatment development of fresh FVP/hemorrhage and the need for a supplement laser to be significantly associated with poor outcome. However, on logistic regression analysis, pre-existing FVP and development of fresh FVP post laser treatment were the only factors which appeared to individually influence outcome. These were similar to previous studies on outcomes of ROP with diode laser and did not appear to be influenced by the use of green laser.[10,22,24,26-28] Eyes with ROP in zone I, have been shown to do better with anti-VEGF as compared to laser.[33] However, the effect of anti-VEGF may be transient and there are increasing number of reports of late recurrences with anti-VEGF monotherapy.[34-36] The present study included eyes with laser monotherapy only and combination with anti-VEGF could have potentially altered the outcome in some of the cases with zone 1 ROP. Posterior zone I ROP has been shown to have very poor outcome with laser alone and a combination treatment with anti-VEGF may be a better option in such eyes.[37]

Very few studies have evaluated the outcomes of green laser in ROP and the present study represents the largest single center study till date [Table 2]. However, the study is not without limitations. The retrospective nature induces inherent observational and inclusion bias. Immaculate record keeping of all ROP babies and review of RetCam images helped in reducing this bias. Another drawback of the study is the lack of a control group. A prospective randomized study is required to compare the safety and efficacy of green and diode laser and support the results of this study. Even though the structural outcomes have been good, functional results, especially the refractive outcomes need to be looked at over a long-term with 532 nm green laser photocoagulation.

Conclusion

In summary, this study reports the safety and efficacy of 532 nm green laser in the treatment of ROP. Eyes treated with green laser had a favorable anatomical outcome in 92.5% across all ROP subtypes including APROP and ROP in zone 1. The results of our study are comparable to the results reported with the use of diode laser. All eyes could be lasered satisfactorily and the presence of TVL did not lead to any additional complications like cataract or hyphema. In a resource limited setting of a developing country, a single laser–the frequency-doubled Nd-YAG 532 nm green laser–which is used for other retinal disorders may also be safely used for treatment of ROP. This study will add more confidence in treating the entire spectrum of ROP with 532 nm green laser.

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Conflicts of interest

There are no conflicts of interest.

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