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Laser Prophylaxis in Patients with Stickler Syndrome

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Purpose: To evaluate the association among laser prophylaxis treatment, retinal detachment (RD), and visual acuity (VA) in patients with Stickler syndrome (SS).

Design: Retrospective comparative case series.

Participants: Patients with SS.

Methods: Patients received extended vitreous base laser (EVBL), nonprotocol laser (NPL), or no laser prophylaxis treatment of any kind.

Main Outcome Measures: The 2 main outcome measures that were examined in these patients were rates of RD and VA.

Results: In this study, 230 eyes of 115 patients were included. Fifty-nine patients were women (51%). The median age at the time of laser prophylaxis treatment was 9.5 years (interquartile range [IQR], 6−13 years), and the median age of patients with RD was 11 years (IQR, 7−18 years). Of the 230 eyes, 92 did not undergo any laser treatment, 9 received NPL treatment, and 129 received EVBL treatment. Of the 129 eyes that underwent EVBL treatment, 4 (3%) had RD, compared with 74 eyes (73%) that had RD and did not receive laser or NPL treatment ($P < 0.001$). Eyes that received EVBL treatment had approximately 8 lines better vision, on average, compared with those that did not receive laser or NPL treatment (−0.86 logarithm of the minimum angle of resolution; 95% confidence interval, −1.1 to −0.64; $P < 0.001$).

Conclusions: Treatment with EVBL seems to reduce the rate of subsequent RD and is associated with better VA in patients with SS. *Ophthalmology Retina 2022;6:263-267 © 2021 by the American Academy of Ophthalmology*

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Stickler syndrome (SS) is an inherited, progressive collagenopathy that was first described in 1965 and is a leading cause of pediatric retinal tears and detachments.[1−9] It has been reported that 10% to 65% of patients with SS have retinal detachment (RD) before the age of 10 years.[3] Some of these RDs are irreparable because of extensive giant retinal tears (GRTs) and proliferative vitreoretinopathy.[10] Retinal tears or detachments in patients with SS have been shown to occur as early as 8 months, and patients with SS require frequent examinations for the detection of RD and prevention of the development of proliferative vitreoretinopathy (PVR), which can result in severe vision loss.[10] Retinal detachments are typically caused by GRT formation near the pars plana. There has been up to an 84% success rate of reattachment and a 33% to 64% improvement in visual acuity (VA) postoperatively, although patients tend to require multiple surgeries.[11,12] Even with anatomic success, vision may still be reduced.

Although some retrospective studies have shown a reduction in RDs after patients have undergone prophylactic treatment through cryotherapy, laser, or scleral buckle, this has not been consistently demonstrated.[13−18] In fact, Monin et al[17] found higher rates of RD after the administration of prophylactic laser. The Cambridge group applied 360° cryotherapy at the ora serrata and observed a decrease of up to 7 fold and 10 fold in unilateral and bilateral RDs, respectively.[13,14] Some studies in which eyes were treated with either focal or 360° of argon laser prophylactically have demonstrated a statistically significant reduction in rhegmatogenous RDs.[15,16,19] However, few studies have analyzed a large sample of patients treated exclusively with laser, and the results of studies with smaller sample sizes have been inconclusive.[17,20]

Replicating the success of prevention with cryotherapy might require a broad, 360° laser, which we termed extended vitreous base laser (EVBL). The purpose of this study is to evaluate the association among laser prophylaxis, RD, and VA in patients with SS.

Methods

This retrospective study of participants was approved by the institutional review board of the University of Chicago (IRB #20-0876). Study participants provided written informed consent. All study protocols adhered to the tenets of the Declaration of Helsinki. The study conformed to the Health Insurance Portability and Accountability Act of 1996 regulations. The study included patients seen between January 1, 2006, and October 6, 2020.

Participants who were included in this study were all patients diagnosed with SS who were evaluated at the University of Chicago Medical Center or Retina Consultants Ltd, Des Plaines,

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Table 1. Baseline Demographic Information of 230 Eyes Stratified by Treatment Status

Baseline Demographic Information	No Laser or NPL (n = 101 Eyes)	EVBL (n = 129 Eyes)	P Value
Female sex, n (%)	44 of 101 (44%)	74 of 129 (58%)	0.065
Age at baseline, yrs, median (IQR)	13 (6–39)	9 (6–14)	0.004
Follow-up duration, yrs, median (IQR)	4 (1–6)	6 (3–7)	0.034
LogMAR at baseline, median (IQR)	0.48 (0.18–2.5)	0.18 (0.1–0.48)	<0.001
Among those without RD at baseline	0.18 (0.1–0.4)	0.18 (0.1–0.4)	
Family history of RD, n (%)	42 of 70 (60%)	64 of 98 (65%)	0.527

EVBL = extended vitreous base laser; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; NPL = nonprotocol laser; RD = retinal detachment.

Illinois. The diagnosis of SS in each patient was made according to previously published clinical diagnostic criteria and, if possible, confirmed by genetic testing.[10]

Our pattern of laser has been to treat from the ora serrata to the equator 360° with laser burn spacing between one half to 1 spot size, which we termed EVBL. This pattern was designed to mimic the adhesion of cryotherapy, which has shown prophylactic success.[13,14] The laser pattern of eyes that had undergone laser prophylaxis treatment but did not follow this pattern of EVBL was termed as nonprotocol laser (NPL). Nonprotocol laser included eyes in which laser was administered only to surround pathology, such as lattice and breaks, or those in which the laser pattern was spaced less densely than 1 burn width or covered lesser area than equator to ora for 360°.

Nonprotocol laser eyes were either treated at other centers or treated by the authors but in a less-thorough pattern in an attempt to avoid pupillary and accommodative dysfunction. Patients and their families were generally offered EVBL at presentation. Some families agreed to EVBL, particularly if the contralateral eye had RD, but some declined. Young patients might have been observed initially, given the lack of prior data on the optimal age at the time of prophylaxis. Extended vitreous base laser treatment was generally administered to both eyes of children under anesthesia and to the contralateral eyes of those who had RD.

The data collected for each patient included relevant demographic information and ocular history, including VA, baseline vitreoretinal pathology, pattern of prophylaxis provided, high myopia (defined as >6.00 diopters [D]), genetic status, duration of follow up from initial presentation to final examination, and retinal status at the latest outpatient follow up. Eyes with RD on presentation were included in the study, considering any previous NPL, EVBL, or no laser. Visual acuity was measured as Snellen acuity and converted to logarithm of the minimum angle of resolution (logMAR). Counting finger vision was estimated at 20/2000 vision (logMAR 2) and hand motion at 20/6000 (logMAR 2.5).[21] For regression purposes, light perception was estimated to be 20/20 000 (logMAR 3) to avoid exclusion from regression analysis. Preverbal children were excluded from the regression analysis of VA if vision was only recorded as fix and follow, but they were included in structural outcome measures. Low vision was defined as logMAR of 1.3 or worse.

For summary data, median and interquartile ranges were reported for continuous variables, and percentages were reported for dichotomous variables. To account for 2 eyes of the same patient, *P* values were reported using the clustered version of the robust (i.e., sandwich) variance estimator or mixed-effects linear regression. Statistical significance was defined as a *P* value of <0.05.

Results

A total of 230 eyes of 115 patients were included. Fifty-nine (51%) patients were women. The median age of the patients in the cohort at baseline was 10 years (range, 6–32 years). The median age at the time of laser prophylaxis was 9.5 years (range, 6–13 years), with a minimum age of 10 months and a maximum age of 57 years. The median age of patients with RD was 11 years (range, 7–18 years). The baseline characteristics stratified by the type of treatment received are provided in Table 1.

Rate of RD

Of the 230 eyes, 92 did not undergo any laser treatment, 9 received NPL treatment, and 129 received EVBL treatment. Of the 129 eyes that underwent EVBL treatment, 4 (3%) had RD, compared with 74 eyes (73%) that had RD and did not receive laser or NPL treatment (Table 2, $P < 0.001$). Twenty percent of patients aged 0 to 5 years, 32% of patients aged 6 to 17 years, and 46% of patients aged ≥18 years had RD ($P = 0.042$). Comparing each subgroup of EVBL, NPL, or no laser, there was a statistically significant difference in having RD between all the groups, except for between the group with no laser treatment and that

Table 2. Retinal Detachment by Laser Status

Retinal Detachment Status	No Laser or NPL (n = 101 Eyes)	EVBL (n = 129 Eyes)	P Value
Retinal detachment	74 (73%)	4 (3%)	<0.001
No detachment	27 (27%)	125 (97%)	

EVBL = extended vitreous base laser; NPL = nonprotocol laser.

Table 3. Retina Complications by Laser Status

Retina Complications	No Laser or NPL (n = 101 Eyes)	EVBL (n = 129 Eyes)	P Value
GRT	22 of 98 (22%)	6 (5%)	<0.001
PVR	16 of 97 (16%)	8 (6%)	0.061
≥2 retina surgeries	37 of 85 (44%)	1 of 123 (1%)	<0.001

EVBL = extended vitreous base laser; GRT = giant retinal tear; NPL = nonprotocol laser; PVR = proliferative vitreoretinopathy.

Table 4. Final Visual Acuity by Laser Treatment

Laser Treatment	VA LogMAR Mean [SD]; Median (IQR)	VA Snellen Mean; Median (IQR)
EVBL (n = 121 eyes)	0.27 [0.27]; 0.18 (0.1–0.4)	20/37; 20/30 (20/25–20/50)
No laser or NPL combined (n = 85 eyes)	0.4 (0.18–2.5)	20/250; 20/50 (20/30 HM)
NPL (n = 9 eyes)	0.4 (0.3–1.3)	20/180; 20/50 (20/40–20/400)
No laser (n = 76 eyes)	0.4 (0.14–2.6)	20/250; 20/50 (20/28 HM)

EVBL = extended vitreous base laser; HM = hand motions; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; NPL = nonprotocol laser; SD = standard deviation; VA= visual acuity.

with NPL treatment. All 9 eyes (100%) that received NPL treatment had RD, and 70.6% of the eyes that were not treated with laser had RD. In addition, there was a significant difference in having ≥2 retina surgeries ($P < 0.001$) and a trend toward having PVR ($P = 0.061$, Table 3) between those who received EVBL treatment and those who did not. Furthermore, there was no significant difference between the mean follow-up duration in patients who had RD and those who did not ($P = 0.19$).

As a surgical referral practice, many eyes presented with RD (n = 66). Of the 164 eyes that presented without RD, 127 underwent EVBL treatment and 37 received no laser or NPL treatment. Two eyes (2%) progressed to RD in the EVBL group, whereas 10 (27%) progressed to RD in the no-laser or NPL group ($P < 0.001$). Of the 12 eyes that developed RD, 4 developed within 1 year, 3 in 2 years, 1 in 3 years, 3 in 4 years, and 1 in 6 years from presentation.

Vision Outcomes

As shown in Tables 4 and 5, patients who underwent EVBL treatment had significantly better final VA than patients with no laser or NPL treatment. Eyes treated with EVBL had about 8 lines better vision, on average, compared with those without laser or NPL treatment (−0.86 logMAR; 95% confidence interval, −1.1 to 0.64; $P < 0.001$). Only 1 eye (<1%) treated with EVBL had low vision, compared with 33% of eyes that did not receive EVBL treatment ($P < 0.001$).

A mixed-effects regression analysis demonstrated the predictors of logMAR VA in this cohort (Table 5). Treatment with EVBL and female sex were associated with improved VA, whereas GRT, number of retina surgeries, and PVR were associated with poorer VA. After adjusting for other factors in a multivariate analysis, only EVBL and the number of retina surgeries remained associated with VA. There were no statistically significant associations between age at baseline, PVR, or GRT.

High Myopia

Of the 230 eyes, information regarding refractive status was available for 215 (93%), of which 105 (49%) had high myopia (>6 D). There was no association between high myopia and RD ($P = 0.75$).

Genetic Testing

The diagnosis of SS was made clinically in most cases. Genetic testing results were available for 11 (9.6%) patients. No statistical analysis was performed because of lack of sufficient data. Nine patients had a documented variation in the type II collagen alpha-1 subunit gene.

Discussion

This study shows that EVBL prophylaxis treatment is associated with not only significantly lower rates of RD but also better VA. In this retrospective review of patients with SS, we observed the overall occurrence of RD in 78 eyes (34%) and a rate of 73% in eyes that received NPL or no laser prophylaxis treatment, which is consistent with previous studies. This association persisted when eyes that presented with RD were excluded. Stickler syndrome confers a lifelong risk of RD. In our series, the youngest patient was 5 months old and the oldest was 52 years old when they experienced their first RD. The median age of patients with RD was 11 years; this finding is similar to that of previous studies that indicated that the majority of RDs occur after

Table 5. Predictors of Final LogMAR Visual Acuity

Predictors of LogMAR Visual Acuity	Regression Coefficient	95% CI	*P* Value	Adjusted Coefficient	95% CI	*P* Value
EVBL	−0.86	−1.1 to −0.64	<0.001	−0.36	−0.65 to −0.07	0.015
Female sex	−0.39	−0.62 to −0.15	0.002	−0.14	−0.38 to 0.10	0.24
Age at baseline	0.01	0.00 to 0.02	0.028	0.00	−0.01 to 0.01	0.91
Family history of RD	−0.04	−0.35 to 0.27	0.82	0.04	−0.21 to 0.29	0.77
GRT	0.68	0.32 to 1.0	<0.001	0.31	−0.12 to 0.73	0.16
PVR	0.79	0.42 to 1.2	<0.001	0.25	−0.18 to 0.67	0.25
Number of retina surgeries	0.24	0.18 to 0.31	<0.001	0.17	0.07 to 0.28	0.001

CI = confidence interval; EVBL = extended vitreous base laser; GRT = giant retinal tear; logMAR = logarithm of the minimum angle of resolution; PVR = proliferative vitreoretinopathy; RD = retinal detachment.

the age of 10 years.[22] There was also a statistically significant difference in the prevalence of RD among the different age groups, with the highest rate being in the adult age group.

The intent of our treatment plan was to target the area of possible GRT formation from the equator to the ora serrata rather than targeting areas of lattice degeneration. Lattice degeneration was surrounded with laser if it was within this zone but not necessarily if it was located more posterior. The goal was to prevent breaks or, if they occurred, to decrease break size and prevent PVR. Of the eyes that underwent EVBL treatment, 97% did not have RD. This number is comparable with the rate of prophylaxis for RD in patients without SS reported in previous studies.[13,14,16] However, this is much more successful than the previous reports of 33% to 50% detachment rates in patients with SS undergoing laser prophylaxis treatment.[17,20] In those studies, it is possible that the laser did not treat the extended vitreous base region strongly enough to prevent a GRT. In our study, 100% (9 of 9) of the eyes that had undergone NPL treatment had RD, which is similar to the incidence of detachment in untreated eyes. Additionally, in our study, the 9 patients who received NPL treatment and had RD had worse median VA (logMAR of 0.40). This suggests that the pattern of laser treatment matters with regard to the success of prophylaxis treatment and preservation of vision, favoring EVBL.

Our pattern of EVBL treatment is designed to replicate the cryotherapy procedure performed by the Cambridge group, which was shown to significantly reduce the rate of RD.[13,14] It is believed that laser prophylaxis may be more widely accessible and is a universal skill compared with cryotherapy. Treatment with EVBL should increase adhesion between the sensory retina and the retina pigment epithelium compared with NPL, which only surrounds the lattice or breaks or is performed in a less-dense or less-thorough pattern. This increased adhesion should limit the extension of a GRT if it were to occur.[23] In addition, there is less conjunctival, anterior chamber, and vitreous inflammation with the use of laser than with the use of cryotherapy.

Consistent with previous data, eyes with GRT, PVR, and multiple surgeries were the most likely to have the poorest vision.[24,25] Eyes not treated with EVBL were significantly more likely to develop a GRT and require $\geq$2 surgeries. This implies that laser treatment prevented the development of a GRT or, if it occurred, prevented the expansion of subsequent RD and the need for multiple surgeries, similar to the finding of a recently published case report.[26]

In addition to having lower rates of RD with EVBL treatment, patients also had better VA and lower rates of low vision. Patients had, on average, 8 lines better vision if they had undergone prophylaxis treatment than if they had not. In our cohort, the eyes of patients who had received NPL treatment had similar median VA as the eyes of those who did not receive laser prophylaxis treatment, likely because they all had RD. This finding is similar to that of a previous study that found that laser was not effective in preventing RD.[17]

The optimal timing of administering EVBL is uncertain. The prevalence of RD in the eyes of patients aged $\leq$5 years was quite high (20%) and only increased with age. Indeed, the youngest patient in this study who developed RD was 5 months old. These data seem consistent with results from the larger cohort, and prophylactic laser treatment may be beneficial even in this younger age group.

There were several limitations to this study. This was a retrospective analysis, and not all data were available for every patient. In our study, a confirmed genetic mutation was not available for majority of the patients. Additionally, there was likely a referral bias, and many patients presented with RD with poor vision at baseline. One of the limitations was that preverbal children were excluded from the analysis of visual outcomes.

One of the strengths of this study is the overall number of patients with SS included. Given that it is a rare disease, a cohort of $>$100 patients is significant, and meaningful conclusions can be derived. In addition, the 8 lines of better vision and the significantly lower rate of RD is of clinical importance. These data certainly constitute at least preliminary evidence that EVBL prophylaxis may prevent RD and is associated with better VA. However, the gold standard would be a randomized controlled trial, which would necessitate a coordinated multicenter effort to compare EVBL with a control group with no laser treatment or a group undergoing NPL treatment, such as lattice-based laser or 3 rows of laser behind the ora serrata. To detect an absolute difference of 20% in the rate of RD at 3 years with 80% power, 35 eyes would be needed per group (assuming that 1 eye per patient is included), and with 90% power, 46 eyes would be needed per group. In the meantime, we recommend considering EVBL prophylaxis for patients with SS to prevent RD and vision loss.

Footnotes and Disclosures

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Disclosures:
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HUMAN SUBJECTS: Human subjects were included in this study. This retrospective study of participants was approved by the institutional review board of the University of Chicago (IRB #20-0876). All research complied with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and adhered to the tenets of the Declaration of Helsinki.

No animals were used in this study.

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Conception and design: Khanna, Rodriguez, Mateo A. Blair, Shapiro, Michael P. Blair

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Abbreviations and Acronyms:
EVBL = extended vitreous base laser; **GRT** = giant retinal tears; **logMAR** = logarithm of the minimum angle of resolution; **NPL** = nonprotocol laser; **PVR** = proliferative vitreoretinopathy; **RD** = retinal detachment; **SS** = Stickler syndrome; **VA** = visual acuity.

Key Words:
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