Early Diagnosis of Ocular Hypertension Using a Low-Intensity Laser Irradiation Test

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Abstract

Objective: We investigated the potential use of low-intensity laser irradiation (LILI) as a diagnostic tool for identifying hypertensive eyes at risk of glaucoma. **Background data:** The diagnosis of early-stage ocular hypertension is particularly difficult to establish. **Methods:** This study of a case series included 123 healthy subjects with normal vision. The intraocular pressure (IOP) was determined before (baseline) and 30 min after a 30-sec irradiation of the limbus area with laser light (780 nm; 7.5 mW; 292 Hz modulation). **Results:** Baseline IOP was >21 mm Hg in 44 of 211 eyes (20.9%), consistent with ocular hypertension. LILI decreased the mean IOP by 6.2 mm Hg (-25.7% ; $p < 0.001$; paired t test) in these eyes. The remaining 167 eyes (79.1%) exhibited a normotensive IOP ≤ 21 mm Hg. LILI reduced the mean IOP by 2.9 mm Hg (-17.1% ; $p < 0.001$) in these eyes, but there were different response patterns: 1) the IOP did not change (27.0%); 2) the IOP was reduced by the same extent in both eyes (32.3%); 3) initial IOP differences between left and right eyes became level and the absolute IOP was reduced to a lower level that was identical in both eyes (18.0%); and 4) the initial difference in IOP between the left and right eye persisted despite LILI (22.7%). **Conclusion:** LILI lowers IOP, even in normotensive eyes. This effect may be useful to determine the individual physiological IOP and to diagnose latent ocular hypertension in eyes with presumably normotensive IOP.

Introduction

GLAUCOMA, A CHRONIC, progressive eye disease, is found in about 2% of the population aged 40 or above. It is estimated that more than 70 million people are affected across the world.¹ Although there are still different classifications, and even definitions, glaucoma is traditionally considered an optic nerve head disease associated with progressive loss of vision and increased intraocular pressure (IOP).^{1,2}

The diagnosis of advanced glaucoma is usually straightforward; it is based on the characteristic pathological excavation of the optic nerve disc (glaucomatous excavation), typical defects of the visual field, and increased IOP. Functional and anatomical alterations are seen as direct consequences of the increased IOP^{3–6} although this association is controversial.^{7–9} An increased IOP is the most important risk factor for damage to the optic nerve. The level of the IOP is, however, not always correlated with the clinical picture causing some diagnostic uncertainty. A “typical” glaucomatous visual field with a glaucomatous excavation and a “statistically normotensive” IOP (≤ 21 mm Hg) may be found

as well as the sole increase in IOP >21 mm Hg without these symptoms, which is termed ocular hypertension. Early diagnosis of glaucoma is even more difficult, in spite of advances in electrophysiology¹⁰ and perimetry,^{11–13} because the individual physiological IOP and its day-to-day variability, as well as other risk factors are unknown.¹⁴ Attempts to diagnose early-stage glaucoma by tonography or provocation tests, like water drinking and administration of caffeine or other drugs, have proved unreliable.^{15,16}

Low-intensity laser irradiation (LILI), which, in contrast to surgical laser applications, does not cause any damage to tissues,¹⁷ has been widely used in experimental and small clinical studies. Recently, we reported that LILI improved vision in patients with both early and advanced stage, age-related macular degeneration.¹⁸

In this study of a case series we examined the potential use of LILI as a tool to determine the individual physiological IOP. The aim was to differentiate between normo- and hypertensive eyes by classifying changes in IOP after irradiation of the limbus area of the eye with a weak laser.

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Materials and Methods

Study subjects

This study of a case series was conducted in accordance with the Helsinki Declaration. Informed consent was obtained in writing from all subjects before enrollment. Data were collected at a single investigational site in Germany and analyzed retrospectively. Study subjects were included in the study if their eyes were apparently healthy (i.e., without obvious pathological findings) as determined by direct ophthalmoscopy and biomicroscopy, in particular without glaucomatous changes of the anterior or posterior eye segments. Subjects were excluded if they presented with eye or systemic disorders or if they were using medication for any disease.

Upon study entry, the baseline IOP was determined using applanation tonometry (Goldmann applanation tonometer; Zeiss, Jena, Germany). Tonometry was repeated 30 min after LILI.

Laser treatment

For LILI a semiconductor laser diode with continuous emission at 780 nm (7.5 mW) was fitted with collimating optics (elliptic spot area 6.28 mm²) in a handheld casing. The laser diode was driven by an apparatus that provided low-frequency switching of the laser beam (292 Hz, 1:1 duty cycle) and automatic power control (Bimed, Munich, Germany). A safe minimal laser power for use in this study was previously determined by examination of enucleated pig eyes.¹⁸

After determining the baseline IOP, each eye (random sequence) was irradiated for 30 sec (0.22 J/cm²) in a circular fashion in the area of the limbus area at a distance of 1 cm. Ten subjects (20 eyes) were randomly selected to receive mock treatment (control group): the laser beam was directed above the nose without contacting the eye, which was in adduction. An acoustical signal every 10 sec was interpreted by the subjects as treatment. During the treatment period, no other therapy was applied. Safety and tolerability of the treatment were determined by interview, direct ophthalmoscopy, and biomicroscopy.

Data analysis

IOP before and 30 min after LILI were compared to calculate the absolute and relative changes in IOP. A paired

t test was performed to examine the statistical significance of changes in IOP.

Results

The physiological variability of the IOP during a 30-min period was first examined in a separate group of 30 subjects (12 men and 18 women with a mean age of 53.7 ± 5.4 years), who did not receive LILI treatment. This initial experiment confirmed that the IOP remained virtually unchanged: mean IOPs were 14.1 ± 0.4 mm Hg and 14.1 ± 0.6 mm Hg at baseline and at the second tonometry 30 min later, respectively.

Variable changes in IOP after LILI

In total, 123 healthy subjects (64 men, 59 women) with a mean age of 59.6 ± 12.3 years were included in the study. All subjects (109 right and 102 left eyes) were treated using LILI. Ten subjects (6 women, 4 men) with a mean age of 53.2 ± 6.1 years were mock treated and served as controls (*n* = 20 eyes).

Two separate groups of subjects were formed based on the baseline IOP, i.e., before treatment with LILI (Table 1).

At baseline, 44/211 eyes (22/123 subjects) had an IOP >21 mm Hg (mean IOP 24.1 mm Hg) consistent with definite ocular hypertension (group 1). The remaining 167/211 eyes (101/123 subjects) exhibited an IOP ≤21 mm Hg (mean IOP 17.0 mm Hg), which was considered statistically "normotensive" (group 2). In this group the IOP was either identical in both eyes (100 of 167 eyes; 59.9%) or different comparing left and right eye (67 of 167 eyes; 40.1%).

Thirty minutes after LILI, the mean IOP decreased from 24.1 to 17.9 mm Hg in hypertensive group 1; this decrease (−25.7%) was statistically significant (*p* < 0.001; pairwise comparison to baseline IOP values). In the "normotensive" group 2 the mean IOP decreased from 17.0 to 14.3 mm Hg 30 min after LILI. Although smaller, this change (−2.9 mm Hg; −17.0%) was still highly significant (*p* < 0.001; pairwise comparison to baseline IOP values). A detailed analysis revealed different response patterns in group 2 (Table 1): in 100 of 167 eyes with identical IOP in both eyes, the mean IOP remained virtually unchanged in 45 eyes (mean IOP of 15.5 mm Hg) before and 30 min after LILI (group 2A), and decreased from 18.3 mm Hg to 13.3 mm Hg (−27.3%; *p* < 0.001) in 55 eyes (group 2B). IOP differed between left and right eyes in 67 eyes 30 min after LILI: 30 eyes exhibited a significant decrease of the mean IOP from 17.0 to 13.3 mm

TABLE 1. INTRAOCULAR PRESSURE (IOP) 30 MIN AFTER LOW-INTENSITY LASER IRRADIATION (LILI) IN EYES CLASSIFIED AS HYPERTENSIVE (GROUP 1, *N* = 44) AND NORMOTENSIVE (GROUP 2, *N* = 167) AT BASELINE

IOP at baseline	Group 1	Group 2 ^a			
	>21 mm Hg	≤21 mm Hg			
Subgroup	1	2A	2B	2C	2D
Eyes, <i>n</i>	44	45	55	30	37
IOP before LILI, mm Hg	24.1	15.5	18.3	17.0	17.2
IOP after LILI, mm Hg	17.9	15.5	13.3	13.3	14.3
Change in IOP, mm Hg	−6.2	0.0	−5.0	−3.7	−2.9
Change in IOP, %	−25.7	0.0	−27.3	−21.8	−16.9

^aPlease see text for an explanation of the subgroups.

TABLE 2. CLASSIFICATION OF OCULAR HYPERTENSION ACCORDING TO THE CHANGE IN INTRAOCULAR PRESSURE (IOP) AFTER LOW-INTENSITY LASER IRRADIATION (LILI) IN SUBJECTS WITH A BASELINE IOP ≤ 21 mm Hg

IOP (mm Hg)		Change in IOP			IOP (mm Hg)		Change in IOP				
Baseline	After LILI	mm Hg	%	Grade (risk)	Baseline	After LILI	mm Hg	%	Grade (risk)		
21	20	1	4.5	0 (normal)	17	16	1	5.9	0 (normal)		
	19	2	9.5			15	2	11.8			
	18	3	14.3			14	3	17.6			
	17	4	19.0			13	4	23.5	I (mild)		
	16	5	23.1	I (mild)		12	5	29.4			
	15	6	28.6			11	6	35.3	II (moderate)		
	14	7	33.3	II (moderate)		10	7	41.2	III (severe)		
	13	8	38.1			9	8	47.1			
	12	9	42.8	III (severe)		8	9	52.9			
	11	10	47.6			16	15	1	6.3	0 (normal)	
	10	11	52.4				14	2	12.5		
	9	12	57.1				13	3	18.8		
	8	13	61.9				12	4	25.0	I (mild)	
	19	1	5.0	0 (normal)			11	5	31.3	II (moderate)	
	20	18	2	10.0			15	10	6	37.5	
17		3	15.0		9	7		43.8	III (severe)		
16		4	20.0	I (mild)	8	8		50.0			
15		5	25.0		14	1		6.7	0 (normal)		
14		6	30.0	II (moderate)	13	2		13.3			
13		7	35.0		12	3		20.0	I (mild)		
12		8	40.0	III (severe)	11	4		26.7			
11		9	45.0		10	5		33.3	II (moderate)		
10		10	50.0		9	6		40.0	III (severe)		
9		11	55.0		8	7		46.7			
8		12	60.0		14	13		1	7.1	0 (normal)	
18		1	5.3	0 (normal)		12		2	14.3		
17		2	10.5			11		3	21.4	I (mild)	
16		3	15.8			10		4	28.6		
15		4	21.1	I (mild)		9		5	35.7	II (moderate)	
19	14	5	26.3		13	8	6	42.9	III (severe)		
	13	6	31.6	II (moderate)		12	1	7.7	0 (normal)		
	12	7	36.8			11	2	15.4			
	11	8	42.1	III (severe)		10	3	23.1	I (mild)		
	10	9	47.4			9	4	30.8	II (moderate)		
	9	10	52.6			8	5	38.5			
	8	11	57.9			12	11	1	8.3	0 (normal)	
	18	17	1	5.6			0 (normal)	10	2	16.7	
		16	2	11.1				9	3	25.0	I (mild)
		15	3	16.7				8	4	33.3	II (moderate)
		14	4	22.2			I (mild)	10	1	9.1	0 (normal)
		13	5	27.8			9	2	18.2		
	12	6	33.3	II (moderate)		10	8	3	27.3	I (mild)	
	11	7	38.9				9	1	10.0	0 (normal)	
	10	8	44.4	III (severe)			8	2	20.0		
9	9	50.0									
8	10	55.6									

Hg (-21.8% ; $p < 0.001$) resulting in identical IOP levels in both eyes (group 2C). The remaining 37 eyes also exhibited a decrease of the mean IOP from 17.2 to 14.3 mm Hg (-16.9% ; $p < 0.001$) but the initial IOP difference between left and right eye remained: the mean IOP was 13.0 and 15.4 mm Hg for right and left eyes, respectively (group 2D).

LILI effects were limited to the irradiated eye only

In a separate group of 35 subjects only one randomly selected eye was irradiated to examine whether any changes occurred also in the nonirradiated eye. The IOP of the non-

irradiated, contralateral eye did not change (data not shown) confirming that the effects of LILI were limited to the irradiated eye only. In addition, the mean IOP did not change 30 min after mock treatment in the control group (14.2 ± 0.5 mm Hg vs. 14.2 ± 0.3 mm Hg at baseline).

Safety and tolerability

The treatment with LILI was overall well accepted by the subjects; the light was still perceived at the selected wavelength but did not blind. No adverse effects were observed.

TABLE 3. CLASSIFICATION OF 167 EYES WITH A BASELINE IOP ≤ 21 mm Hg (GROUP 2, SEE TABLE 1) ACCORDING TO THE RESULTS OF THE LOW-INTENSITY LASER IRRADIATION (LILI) TEST

	IOP decrease (%)			
	<20	20–29	30–39	≥ 40
Grade	0	I	II	III
No. of eyes (%)	116 (69.5)	25 (15.0)	21 (12.5)	5 (3.0)

Discussion

The biological effects of LILI have been studied in a variety of settings but only a few experimental studies have addressed ophthalmologic diseases before.¹⁸ We report here for the first time that LILI of the limbus area of the eye may lower the IOP. The laser power used here does not cause thermal damage and may well reach the ciliary body and the trabecular meshwork as previously shown.¹⁸ The molecular mechanisms translating laser irradiation into biological effects are largely unknown but it is conceivable the laser photons may cause cell membrane hyperpolarization promoting the contractility of trabecular meshwork and ciliary muscle cells.¹⁹

The IOP is the result of a complex balance of the production and outflow of the aqueous humor in the eye. There is considerable inter-individual variation of the physiological level of the IOP, and this level cannot be readily determined. Even a “statistically normotensive” IOP within the range of 10 to 21 mm Hg may cause glaucomatous damage to particularly susceptible eyes with much lower physiological levels of IOP. This is consistent with the occurrence of normal tension glaucoma.

The major result of this study is the finding that the IOP can be lowered by LILI, presumably to the individual physiological level. To verify that the physiological IOP has been identified, it may be necessary to repeat LILI until the IOP cannot be reduced further. A study limitation is the lack of long-term observations after LILI. It is currently unknown, how long the effects of a single LILI treatment last. There are several potential implications: 1) latent ocular hypertension defined as a nonphysiological IOP within the “normotensive” range, can be detected before it may lead to glaucomatous damage, 2) an individual target IOP can be defined for antiglaucoma therapy, and 3) LILI may even be useful to distinguish glaucomatous from nonglaucomatous optic atrophy (remains to be shown).

LILI decreased IOP

The largest decrease in IOP (–26%) was observed in eyes with a pathological baseline IOP of >21 mm Hg which exhibited ocular hypertension without damage. However, LILI also decreased IOP in most eyes (73%) with a “normotensive” baseline IOP reaching a mean level of 14.1 mm Hg in this group, which is in agreement with the accepted population-based normative IOP.¹⁶ Different patterns of IOP reduction suggested that 1) the physiological IOP may be lower in many, yet apparently normal eyes and that 2) these physiological IOP levels may differ between left and right

eye or, conversely, the IOP may have been elevated in one eye only at baseline examination. Moreover, the effects of LILI were limited to the treated eye only, consistent with the independent blood supply and innervation of the eyes. Systemic effects of LILI were therefore not detectable.

LILI may be useful to classify ocular hypertension

The relative (not absolute) reduction of IOP compared to baseline values may be exploited for diagnostic purposes. We hypothesized, for example, that a baseline IOP of 12 mm Hg would be a potential risk factor for glaucoma if the IOP was 8 mm Hg after LILI. In this case, the baseline value was increased by 33.3%. In comparison, a decrease from 21 to 17 mm Hg (i.e., 4 mm Hg or 19.0%) may raise no concern. This hypothesis was based on the finding that some eyes are particularly susceptible to glaucomatous damage, although they exhibit only low, “statistically normotensive” IOP levels within the range of 10 to 21 mm Hg. The prevalence of normal tension glaucoma is 2%.^{20–22}

The diagnostic “LILI test” introduced here, may be particularly useful to detect latent ocular hypertension in eyes with apparently “normotensive” but potentially nonphysiological IOP, if ocular hypertension is associated with an open angle. Eyes with ocular hypertension may be at risk of developing glaucoma later on. Untreated ocular hypertension leads to glaucoma in 9.5% of cases.^{6,20,23} Eyes with ocular hypertension should be followed closely and treated early as soon as first signs of glaucomatous damage appear, with a therapeutic target IOP at the level observed after LILI.

Based on the relative reduction of baseline IOP after LILI, we propose a classification of ocular hypertension to be validated in future prospective clinical trials: a relative difference $<20\%$ between IOPs before and after LILI would be considered normal variation (grade 0). Differences of 20–29% (grade I) and 30–39% (grade II) would correspond to mild and moderate ocular hypertension, respectively. A marked difference equal or greater than 40% would designate severe ocular hypertension (grade III). This classification could also be applied to eyes with latent ocular hypertension (baseline IOP ranging from 10 to 21 mm Hg) as shown in Table 2.

According to this classification, no ocular hypertension was found in 116 of 167 eyes (69.5%) of group 2 (Table 3). The remaining 51 eyes (30.5%) are classified as eyes with mild (grade I), moderate (grade II), or severe (grade III) latent ocular hypertension relative to their lower physiological IOP. Notably, according to current terminology these eyes were normotensive without any further differentiation.

Latent ocular hypertension was found in 30.5% of eyes with “normotensive” IOP (Table 3). This may be rather frequent in comparison to published epidemiological data. It cannot be ruled out that the upper threshold for normal variation ($<20\%$ change in IOP) is too low. It should be noted that this classification is based on the limited data set from the present study. The classification may contain minor errors because baseline IOP may vary. However, the prevalence of glaucoma with permanent damage is estimated to range from 1.2% to 5.6%; in more than half of these patients, their eyes exhibited a still “normotensive” IOP of ≤ 21 mm Hg.²² The frequency of severe latent ocular hypertension (grade III) in group 2 (Table 3) is in agreement with this observation.

Conclusion and Summary

Our data suggested that LILI can reduce IOP in hypertensive and normotensive eyes. This effect may be exploited for a diagnostic test useful for the detection of ocular hypertension assuming that LILI uncovers the true physiological IOP. The LILI test may also provide valuable information about the individual therapeutic target IOP for treatment of ocular hypertension and glaucoma. Moreover, LILI itself may be an additional tool to treat ocular hypertension and glaucoma. On the basis of this pilot study, multi-center clinical trials are now required to confirm these data.

Disclosure Statement

No competing financial interests exist.

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