Comparison of Conventional Pattern and Novel Navigated Panretinal Photocoagulation in Proliferative Diabetic Retinopathy

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Purpose. To compare the laser spot quality between the conventional slit lamp pattern laser (PASCAL) and the navigated pattern laser (NAVILAS) for panretinal photocoagulation (PRP).

Methods. Prospective randomized interventional trial of 73 eyes (51 patients) with high-risk proliferative diabetic retinopathy. Eyes underwent PRP using 30-ms pulse duration with either PASCAL (16 eyes) or NAVILAS laser (21 eyes), or 100-ms pulse duration with either PASCAL (16 eyes) or NAVILAS laser (20 eyes). Fundus color images of all quadrants were taken 5 minutes after treatment. Laser burn size (major and minor diameter and area) and ellipticity (ratio of minor to major axis) were analyzed across the retina. Treatment time and pain were compared between both groups.

Results. The burn size variation in navigated laser 30 ms, 100 ms, and conventional pattern 30 ms and single-spot 100 ms laser was 22%, 24%, 21%, and 35%, respectively. The variation of the laser burn area near the arcade for NAVILAS and for PASCAL was 29% and 22%, respectively ($P < 0.01$). Closer to the equator, burns from the NAVILAS showed even smaller variation of 15% compared with 25% with PASCAL ($P < 0.005$). Laser spots from PASCAL exhibited an increasing elliptical shape toward the periphery, whereas NAVILAS laser spots tended to be more uniform all over the retina. Average treatment duration and pain experience was less with navigated laser compared with pattern laser ($P \leq 0.05$).

Conclusions. Navigated laser treatment achieves more uniform laser burns with less pain during shorter treatment duration in comparison with conventional pattern laser.

Keywords: panretinal photocoagulation, NAVILAS, navigated laser, slit-lamp laser system, PASCAL

Photocoagulation of the retina was introduced first by Meyer-Schwickerath in the 1940s.[1] Since the Diabetic Retinopathy Study[2] and the Early Treatment Diabetic Retinopathy Study (ETDRS) reports,[3,4] conventional laser photocoagulation through the slit lamp or indirect ophthalmoscope delivery has been the standard of care for proliferative diabetic retinopathy. Based on the ETDRS criteria, panretinal photocoagulation (PRP) uses conventional lasers where typically a 500-μm spot is applied to the retina with pulse duration of 0.1 to 0.2 seconds.[3] Positioning of conventional laser spots is performed manually by moving and tilting contact lens, slit lamp, and aiming beam joystick.

During the following years, sequential improvements took place, including introduction of yellow, green, and diode lasers with various advantages of each wavelength.[5–7] In 2006, the pattern-scanning laser photocoagulation technique was introduced, with a reduction in pulse duration of each laser spot from typical 100 ms down to 10 ms to minimize the time needed to apply multiple laser treatment spots in a preselected, fixed pattern during which the eye can move.[8] The introduction of pattern-scanning laser systems, where the treating ophthalmologist only positions a regular pattern of laser spots, induced a significant reduction in treatment time, as well as the patient's pain perception.[9–11] However, this improvement required the reduction of the pulse duration to 0.02 to 0.03 seconds, representing a change from the ETDRS protocol. All other aspects of application remain the same as with standard conventional laser (imaging, illumination, and spot positioning). Navigated laser photocoagulation was introduced in 2009 initially for focal laser treatment, with an ability to perform color, infrared, and fluorescence angiography imaging, digital treatment planning of desired treatment location based on fundus images, and subsequent image focal laser treatment to compensate eye movement. Navigation functions offered by this laser for focal treatment, such as laser prepositioning by computer assistance, have been studied extensively and have shown significant increase in treatment accuracy compared with all currently existing laser systems[12] and reducing the need of laser retreatments by 42%.[13]

Recently, navigated photocoagulation was extended with navigated panretinal photocoagulation (nPRP), which allows imaging and the positioning of single and multispot laser patterns up to far periphery with continuous prepositioning of the laser beam position relative to eye movements. As a result of stabilization of the laser onto the retina, multispot treatment patterns may now be applied with the well-known longer pulse

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durations, such as of 0.1 seconds and longer. This makes following the ETDRS protocol possible even with the pattern laser photocoagulation technique. Furthermore, navigated laser treatment minimizes patient light exposure by using continuous infrared imaging and limiting visible light to image captures to assess treatment evaluation images.

The aim of this study was to assess safety and feasibility of navigated PRP in proliferative diabetic retinopathy and to compare the spot quality (ellipticity, burn intensity, burn area) between the conventional slit lamp–based pattern laser and the navigated pattern laser, depending on the location on the retina and pulse duration used. As the imaging and laser-delivery principles for the navigated laser system and the conventional slit lamp–based lasers differ, we hypothesize that the laser spot quality may also differ between the two systems. The association between laser spot shape and therapeutic efficacy in PRP was not part of this laser delivery and laser tissue interaction study.

METHODS

Study Design

This prospective study was performed at the LV Prasad Eye Institute, Hyderabad, India, and at the King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, from January 2013 to May 2013. Patients either received navigated laser or conventional pattern laser. Prior approval from the institutional review boards at both institutes was granted and informed consent was obtained from each study subject. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Patients

Patients were prospectively enrolled at both sites. Inclusion criteria included patients (aged ≥18 years) with type 1 or 2 diabetes and high-risk proliferative diabetic retinopathy (PDR), which was defined as the presence of neovascularization (NVD) at the disc, presence of NVD associated with vitreous or preretinal hemorrhage, or neovascularization elsewhere of more than half the disc area associated with vitreous or preretinal hemorrhage. Patients with low-risk PDR features with special indications, such as monocular, poor compliance, or pregnancy, were excluded. Further exclusion criteria were any history of prior panretinal laser treatment or vitrectomy in the study eye; history of anti-VEGF injections received within 2 months; evidence of center-involved diabetic macular edema; media opacities, such as significant cataract, corneal opacity, or vitreous hemorrhage obscuring fundus details; coagulation abnormalities; or use of anticoagulant other than aspirin.

All participants underwent comprehensive ophthalmic examinations, including visual acuity testing, slit-lamp biomicroscopy, IOP measurement using Goldmann applanation tonometer, and dilated fundoscopic examination. Color fundus photographs and fluorescein angiography were performed at baseline before laser photocoagulation.

Laser Procedure

Laser photocoagulation was performed using either the NAVILAS (OD-OS GmbH, Berlin, Germany) laser system for those randomized to navigated PRP arms or PASCAL (TopCon, Tokyo, Japan) for those randomized to the conventional single-spot or pattern PRP arm. The same physicians (JC, IK) performed the treatments using both devices. Both retina specialists have extensive experience with the two devices. Subjects were enrolled and randomized into four groups: group 1, navigated PRP using short pulse duration patterns (20–30 ms); group 2, conventional PRP using short pulse duration patterns (20–30 ms); group 3, navigated laser using pulse duration of 100 to 200 ms; and group 4, conventional single-spot photocoagulation using pulse duration of 100 to 200 ms.

Laser parameters were set as follows: laser power to achieve a greyish-white burn, spot size of 300 μm for navigated groups and 200 μm for conventional groups; and 1.5 burn width spacing for patterns and pulse duration according to treatment group. For all navigated treatments, proprietary lens with no spot magnification was used after 0.5% propacaine eye drop for topical anesthesia. For all conventional photocoagulation treatments, Mainster 165 PRP lens (Ocular Instruments, Inc., Bellevue, WA, USA) with magnification of 1.96 times was used, giving a corrected spot size on the retina of 392 μm.

Whereas the navigated laser delivers the beam through ophthalmoscopic optics, based on a scanning slit projecting a reflex free image onto a 2-dimensional digital image sensor with an erect image, conventional lasers use a microscope with a manually moved slit while seeing the image upside down. Both navigated and conventional pattern lasers use a contact lens to image the retina up to the far periphery. Although the navigated laser uses a proprietary lens, several different types and magnifications are available for the conventional lasers. The differences between navigated and conventional lasers also include the method of laser beam positioning. With slit lamp–based lasers, the laser beam is steered manually with slight movements of a contact lens and slit lamp (joystick) to reach the far periphery. In contrast, the navigated laser provides a pattern positioning, independent from the imaging by using galvanometer scanners controlled by the operator via elements on the system base joystick.

Treatment Time and Pain Perception

Videos of treatment sessions were recorded for analysis of treatment time; where not available, an assistant recorded treatment time. Treatment time was calculated from the first lasered spot to the last lasered spot. Initial time to adjust position of the head, focusing into the retina was not calculated.

A visual analogue scale (VAS) was used to evaluate pain experience 5 minutes after the laser treatment. The VAS consists of a 10-cm line, with 0 on one end representing no pain and 10 on the other representing the worst pain ever experienced.

Laser Spot Variation Evaluation

Five minutes after the laser session, color images of the retina up to the equator were obtained for all the subjects so as to evaluate the characteristics of the laser burns. These images documented and allowed the comparison of laser burn characteristics in all groups. Images of 10 to 20 randomly selected laser burns from each patient were marked and analyzed using the digital image analysis software ImageJ (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). For patients from the short pulse groups, 10 spots were selected closer to the arcades and 10 spots were selected as much in the periphery as possible. In the 100-ms groups, 20 spots were selected in proximity to the arcades. An ellipse was drawn around the visible boundaries of selected clear laser spots (Fig. 1A). Longest and shortest axis of the ellipse were measured in pixel coordinates and converted into physical coordinates using navigated photocoagulator calibration factors provided by OD-OS GmbH (Berlin, Germany). *Laser burn area* was used to evaluate the variances of the actual spot size visible on the

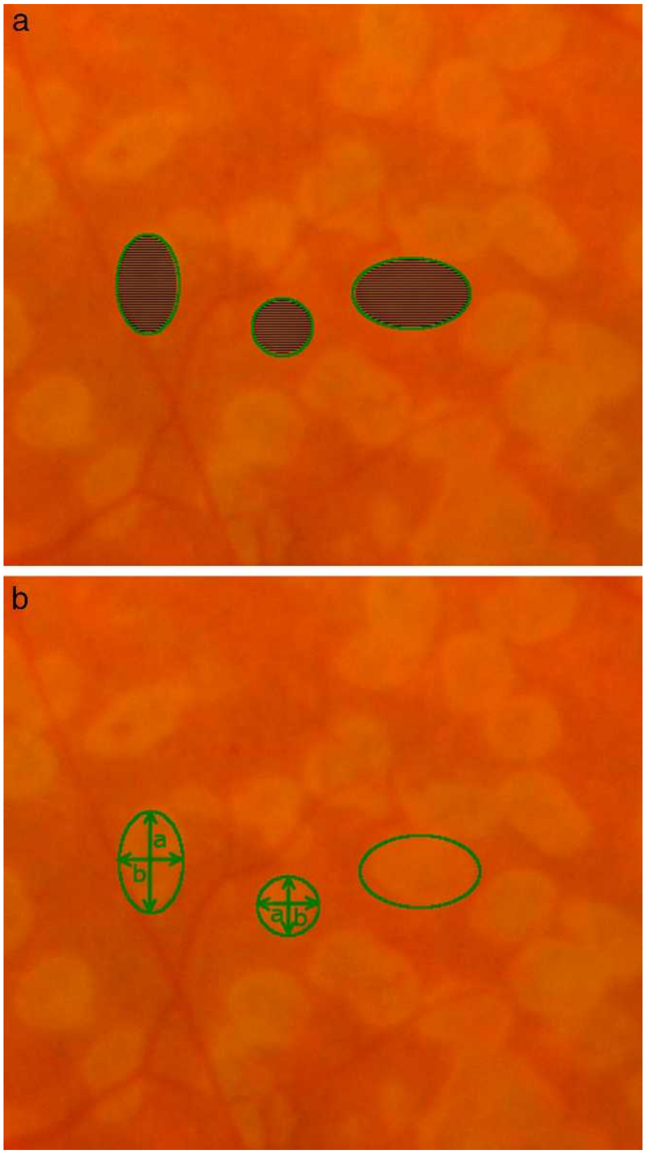

FIGURE 1. Spot measurement. An ellipse was drawn around the visible boundaries of selected clear laser spots from color fundus photos after retinal photocoagulation (**a**). Longest and shortest axis of the ellipse were measured in pixel coordinates and converted into physical coordinates (**b**). Laser burn area from color fundus photos was used to evaluate the variances of the actual spot size visible on the retina. It is calculated for each effect analyzed by use of formula 1 (with "*a*" being axis 1 and "*b*" being axis 2).

retina. Because the burn shape is not geometrically circular, instead of using the spot size directly, the laser burn area was used. It is calculated for each effect analyzed by use of formula 1 (with "*a*" being axis 1 and "*b*" being axis 2) (Fig. 1B).

$$Ae = \pi \times a/2 \times b/2 \qquad (1)$$

Instead of using the spot size directly (only one diameter obtained from measured ellipse), the laser burn area was used, as the area compensates for the elliptical forms of the applied spots. The *ellipticity* was additionally evaluated, defined by the ratio of larger diameter divided by smaller diameter. The closer this value is to 1, the more circular (more uniform) the laser burn is shaped.

TABLE 1. Distribution of Patients Among Groups and Mean Number of Laser Spots

	No. Eyes (Patients)	Age	No. Spots ± SD
30 ms			
Navigated pattern	21 (12)	54 ± 7	1547 ± 466
Conventional pattern	16 (11)	53 ± 11	1234 ± 700
100 ms			
Navigated pattern	20 (17)	53 ± 10	1152 ± 469
Conventional single spot	16 (11)	50 ± 8	1009 ± 298

The outcome measures therefore included the size and the ellipticity of the laser burns near the arcades in all four groups and near the equator in the long pulse groups. In addition, treatment time and patient's pain experience were evaluated. Statistical significances were calculated by using Student's *t*-test for pain, treatment time, ellipticity, and F-test for evaluation of significance in laser burn area variances.

All data were collected in a MS-Excel 2010 spreadsheet (Microsoft Corporation, Redmond, WA, USA) and analyzed using the Statistical Package R (Foundation for Statistical Computing, Vienna, Austria). Image data were collected and evaluated using the digital image analysis software Image J.

RESULTS

Patients and Laser Procedure

A total of 73 eyes (47 from LV Prasad Eye Institute, and 26 eyes from King Khaled Eye Specialist Hospital) of 51 patients were treated with panretinal photocoagulation. The group had a mean age of 53 ± 9 years. Table 1 shows distribution of patients among groups and mean number of laser spots. All treatments were uneventful, with no adverse event observed during the treatments. Figures 2A–D show examples of treatments representing all study groups.

Treatment Time

The average treatment duration for PRP was shorter with navigated PRP (8 minutes 5 seconds) compared with pattern laser PRP (11 minutes 28 seconds) ($P = 0.04$), even though 25% more spots were placed with navigated 30-ms laser as compared with conventional laser and 14% more spots were placed with navigated 100-ms groups. To compensate for the different amount of spot applied in each group for statistical purposes, the time required per 100 spots was calculated and is shown in Table 2 and Figure 3. The median time per 100 spots was 34 seconds with the navigated 30-ms pattern, which is significantly less compared with the median time of 60 seconds required with conventional pattern laser in the 30-ms treatment arm ($P = 0.03$). There was no significant difference between groups in the 100-ms treatment arm.

Pain Perception

As indicated in Table 3, the pain experience was consistently lower with navigated laser than with the conventional laser, independent from pulse duration used ($P = 0.8$). Patients treated with conventional pattern laser using 30-ms pulses experienced insignificantly less pain than the patients with the conventional laser using single spots with 100-ms pulse duration (1.6 ± 1.42 and 2.4 ± 2.0) ($P = 0.2$). Statistical difference for pain reduction with the navigated laser could be

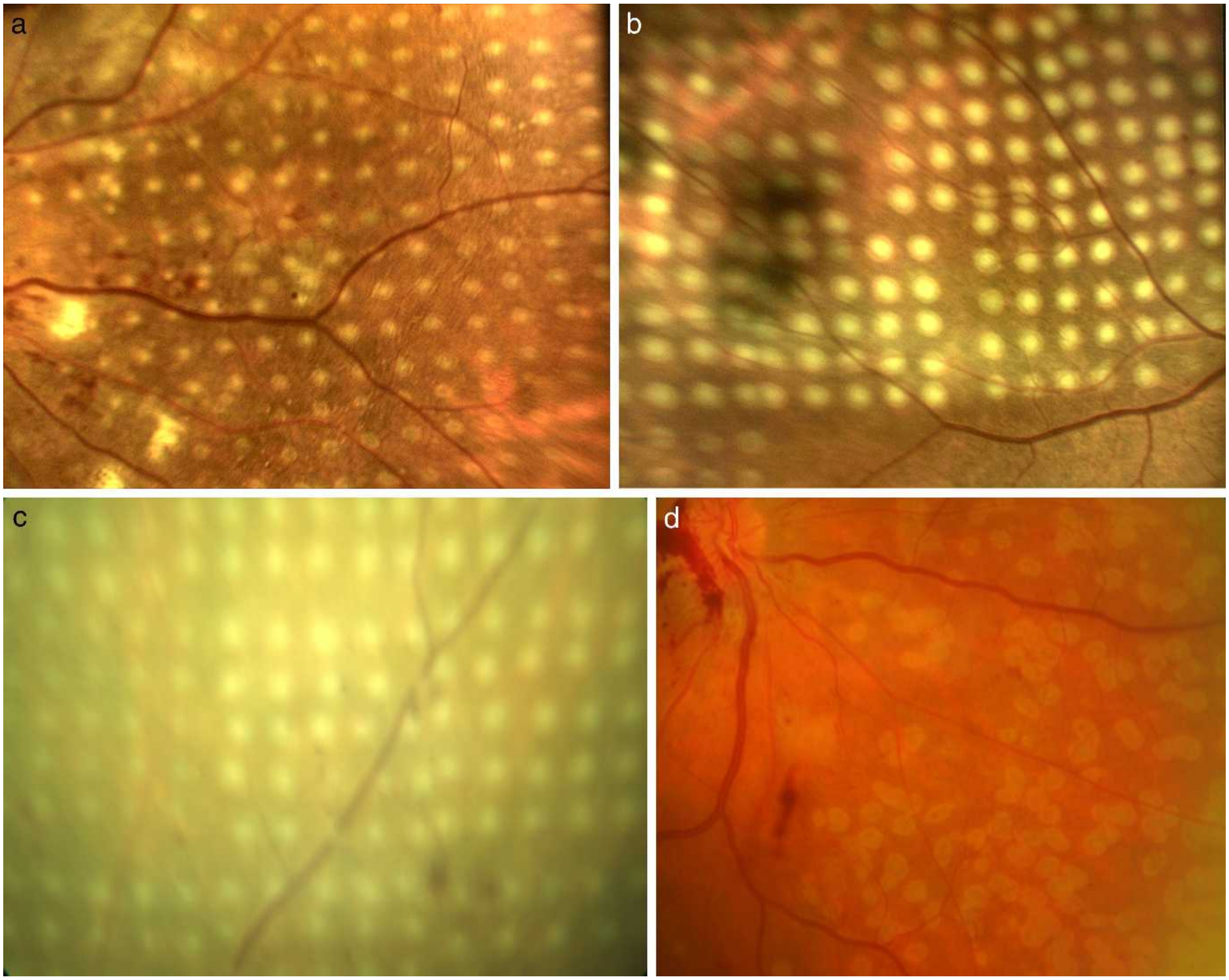

Figure 2. Panretinal laser photocoagulation. Color fundus photograph of navigated pattern panretinal laser photocoagulation in an eye with proliferative diabetic retinopathy using NAVILAS photocoagulator (30-ms pulse duration) (**a**), PASCAL photocoagulator (30-ms pulse duration) (**b**), NAVILAS photocoagulator (100-ms pulse duration) (**c**), and PASCAL photocoagulator (100-ms pulse duration) (**d**).

noted only for patterns performed with spot durations of 100 ms ($P = 0.02$).

Laser Spot Variation Evaluation

Laser Burn Area. A smaller laser burn area (average spot sizes) was obtained with shorter pulses with both laser delivery systems. The variation of the laser burn area among the different groups was not significant except for the smaller variation of laser burns with navigated laser using 100 ms compared with the laser burn variation with conventional laser using 100-ms laser spots ($P < 0.01$). The variation among the groups in navigated laser (30 ms), navigated laser (100 ms), conventional pattern (30 ms), and conventional single spot (100 ms) was 22%, 24%, 21%, and 35%, respectively (Table 4).

Similar analysis was done to assess the variation of laser burn area (spot size) between areas in proximity to arcades and areas close to the equator. As it is not assumed to see differences within the same system when using different pulse durations, this analysis was conducted only for the 30-ms pulse duration group for the different laser delivery systems.

The variation of the laser burn area near the arcade for navigated pattern laser and for the conventional pattern laser was 29% and 22%, respectively ($P < 0.01$). In the area closer to the equator, laser burns from the navigated laser showed even more significantly smaller variation of 15% compared with 25% with laser burns applied with the conventional laser system ($P < 0.005$) (Table 5).

Ellipticity of Laser Burns. With the assumption that the best shape of the laser burns is a circle,[14] the analysis is based on the ellipticity of the laser burn. The ellipticity is obtained by dividing the larger diameter by the smaller diameter (and not the horizontal diameter divided by the vertical diameter). The closer the value is to 1, the more circular is the laser burn.

Figure 4 describes the ellipticity of laser spots analyzed for each laser delivery system in both pulse widths and

Table 2. Summary of Treatment Time for Navigated and Conventional Laser

	Navigated Laser ± SD, s	Conventional Laser ± SD, s	*P*
30 ms	34 ± 20	60 ± 133	0.03
100 ms	87 ± 47	76 ± 69	0.4

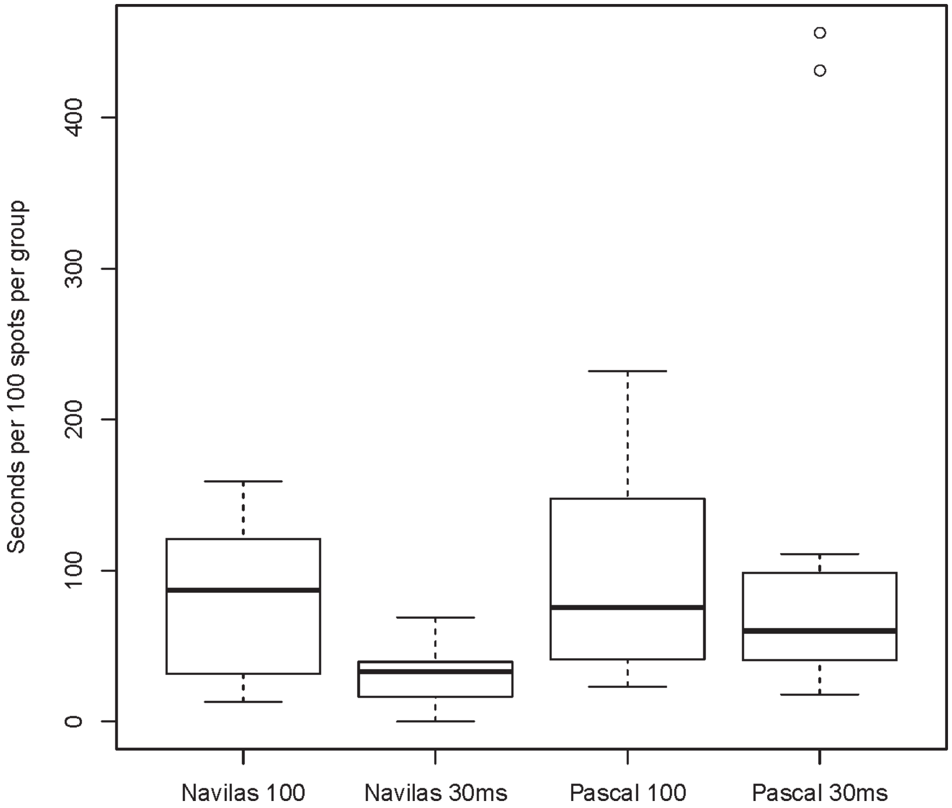

Figure 3. Photocoagulation treatment times. Graph depicting times required per 100 photocoagulation spots in every study arm. The median time per 100 spots in navigated 30-ms arm was 34 seconds, which is significantly shorter compared with 60 seconds required with conventional pattern laser ($P = 0.03$). There was no significant difference between groups in the 100-ms treatment arm.

demonstrates that the analyzed systems do not show differences when using 30-ms pulse durations. However, the navigated laser with 100-ms pulse durations shows significantly more circular spots than the conventional laser with 100-ms pulse duration. Both systems show more circular spots when longer pulse duration is used.

As shown in Figure 5, laser spots from the conventional laser exhibited an increasing elliptical shape toward the periphery, whereas the navigated laser spots tended to be more uniform all over the retina. (Ellipticity of laser spots increases from the arcades with compression ratios of 0.94 and 0.91 for navigated and conventional treatment, respectively, $P < 0.01$, to the equator with compression ratios of 0.83 and 0.81 for navigated and conventional treatment, respectively, $P = 0.02$.)

Discussion

This study introduces the concept of navigated PRP and offers several observations in comparison with currently used multispot laser photocoagulation techniques. We herein demonstrate that the navigated laser system achieves more uniform laser spots with less variation in size compared with the conventional pattern laser. The navigated laser appears to be safe, faster, and associated with less pain when using certain treatment parameters in comparison with conventional laser during treatment of similar sets of eyes.

One of the main outcomes of this study was laser tissue interaction of the two photocoagulation methods. Using both systems, the laser spot characteristics depend on the location of the spots on the retina and the pulse duration. When using short pulses, both systems show smaller laser burn area (spot size) variation. However, when using shorter pulses, both systems produce more elliptical laser spots.

The smaller variation of laser burn area when using short pulse duration can be explained by the reduced impact of eye movements on laser exposure. The shorter the pulse, the fewer movement artifacts occur. This also may explain why the navigated approach shows better results in spot size variation when using longer pulse durations as compared with the conventional pattern laser with longer pulse durations, as navigation compensates for eye movements. Differences in thermal expansion of the spots may have an additional impact. Each specific spot on the retina has slightly different characteristics in terms of RPE (thickness, amount of melanin, blood flow in area around spot), which may have an impact on

Table 3. Pain Experience Among All Groups Using Visual Analog Scale

	Navigated Laser ± SD	Conventional Laser ± SD	Value for Difference *P*
30 ms	0.9 ± 1.14	1.6 ± 1.41	0.1
100 ms	1.0 ± 0.91	2.4 ± 1.99	0.02
Value for difference *P*	0.8	0.2	

Table 4. Variation of Laser Spot Area Within Groups

	Navigated Laser, %	Conventional Laser, %	*P*
30 ms	22	21	0.23
100 ms	24	35	<0.001

Table 5. Variation of Laser Burn Area Comparison of Different Retinal Regions

	Navigated Laser, %	Conventional Laser, %	*P*
Retinal arcades	29	22	<0.01
Retinal equator	15	25	<0.005

the thermal expansion of the spot. The shorter the pulse, however, the less impact such parameters have on the spot size.

The initial shape (ellipticity) of the spot is defined by aberrations of the optical systems, whereas the thermal expansion may potentially be influenced by the initial shape of the laser spot.

In both systems, the spots applied to the far periphery suffer from a higher ellipticity, with the navigated laser having less of this effect and showing in general more circular spots. The increasing ellipticity can be explained by the characteristics of refraction of the lens. To image the far periphery, the light must pass the outer segments of the lens, where distortions are less compensated. This effect applies to all optical concepts and can therefore be observed in both systems. For the navigated laser, the contact lens has aspheric surfaces specifically designed for peripheral imaging and treatment with the navigated photocoagulator. With the conventional laser systems, large movements of the contact lens and the slit lamp are usually used to visualize the far periphery. These larger movements cause tilt of the lens versus the optical axis of the system, resulting in astigmatic spot imaging.[14] Because the lens of the navigated laser requires less tilt to reach the far periphery, the astigmatism effects are reduced/minimized.

Treatment time tended to be shorter when using the navigated laser. This can be explained with the navigated treatment method. Once the system is "locked" into the correct position with a clear image, only a few more actions are needed to apply a large series of spots, thus supporting an increase of treatment speed with at least the same and even better results when visually evaluating the laser spot quality results. However, especially the first step of initial positioning involves a learning curve with the navigated system and may require some time for inexperienced users. Larger retinal area can be visualized with a wide-field lens used for navigated PRP requiring less lens positioning and aiming beam maneuvering. Illuminating larger areas (with white light) on slit-lamp laser delivery increases patient discomfort. Depth focusing in the "*z*"-axis thus becomes the only time-consuming part in the nPRP process. With conventional laser, the illuminated area has a slit shape that is smaller. Therefore, in addition to depth focusing, more manipulation is needed, including constant manual prepositioning in the "*x-y*"-axes.

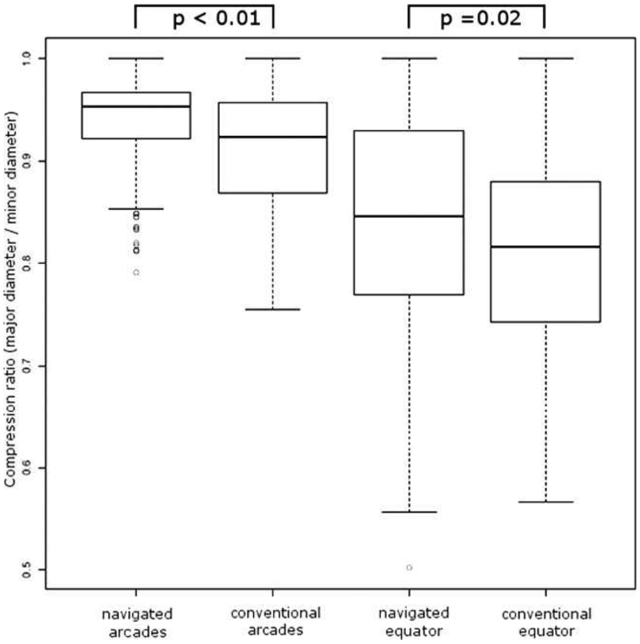

Figure 4. Spot analysis. Graph showing ellipticity measurement of a single laser spot. It demonstrates that conventional pattern laser spots exhibited an increasing elliptical shape toward the periphery, whereas the navigated pattern laser spots tended to be more uniform all over the retina.

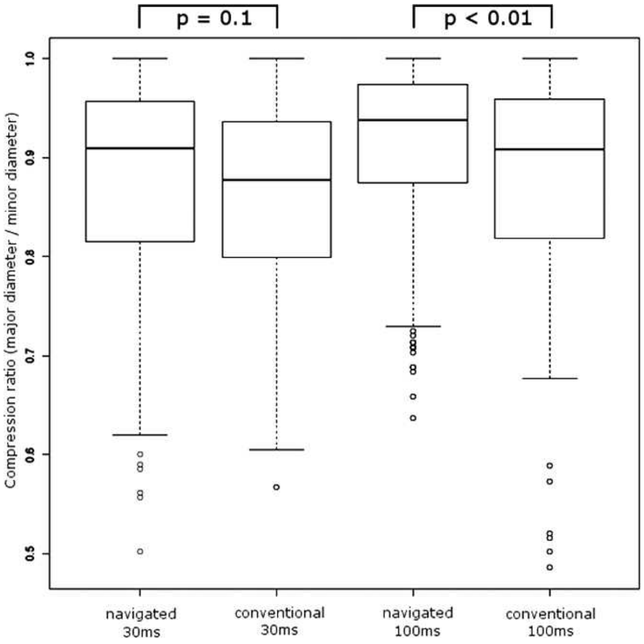

Figure 5. Spot analysis. Graph showing ellipticity of laser spots analyzed for each treatment arm. It demonstrates no differences among pattern photocoagulators when using 30-ms pulse-duration treatments. However, the navigated laser with 100-ms pulse durations shows significantly more circular spots than conventional laser with 100-ms pulse duration. Both systems show more circular spots when longer pulse duration is used.

Level of subjective pain was similar between both lasers. Only the conventional pattern laser treatment showed significantly more pain when applying spots with 100 ms. This result is supported by previous studies about the conventional pattern treatment systems.[9,10] The navigated laser shows a small benefit in terms of pain. The provided infrared treatment in navigated systems may induce this additional benefit.

Clinical implications of laser burn area variation and also ellipticity may be relevant only for treatments closer to the arcades or in selective or targeted treatments. It is assumed that very circular spots have less or at least more regular expansion over time. Thus, a treatment plan can correctly include this expansion to minimize collateral damage. However, this impact for therapeutic efficacy needs to be further analyzed over time. Currently, there are no data that "ellipticity" of the laser spot may have some therapeutic relevance for PRP. However, with increasing ellipticity, the spot area is subject to change.

Additionally, with changing spot area and maintaining pulse duration and power, the energy density changes. If the first burn is done with circular spot and an appropriate power, and the second spot is more peripheral and thus more elliptical with an uncontrollable spot area development (area turns to be larger), the power may not be sufficient to create the desired effect: ablation of ischemic retina. The standard reaction would be to turn the power up once no more effect is visible. However, turning back to other retinal areas, the spot ellipticity decreases and the intensity may now become excessive. If the spot is applied in a relatively slow repeat mode where spots are placed one by one, this can be avoided easily. However, with the pattern laser, a relatively large area would be treated with the wrong power. Nevertheless, there are no published data that explain the effect of the different laser spot shape on therapeutic efficacy of PRP. As seen in clinical practice, retinal laser photocoagulation using indirect ophthalmoscope delivery provides similar clinical efficacy in spite of irregular burns.

In conclusion, our study reports on navigated PRP as a new way to perform PRP. It is a safe and feasible method with some benefits over the conventional pattern photocoagulation relating to treatment time, pain perception, and laser spot characteristics. Navigated laser treatment achieves more uniform laser burns with less pain experienced by patients during a shorter treatment duration in comparison with the currently mostly used pattern laser system. The navigated laser could be a new alternative for future PRP. Further studies are ongoing to compare the clinical efficacy between both laser delivery systems.

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