Evaluation of the efficacy of laser peripheral iridoplasty in reversing the darkroom provocative test result in Chinese patients with primary angle closure status post laser iridotomy

Ping Huang, Ling-Ling Wu

Department of Ophthalmology, Peking University Third Hospital, Key Laboratory of Vision Loss and Restoration, Ministry of Education, Beijing 100191, China

Correspondence to: Ling-Ling Wu. Department of Ophthalmology, Peking University Third Hospital, Beijing 100191, China. wullc@hotmail.com

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Abstract

- AIM: To investigate the efficacy and safety of krypton laser peripheral iridoplasty (LPIP) for Chinese patients with primary angle closure (PAC) or primary angle-closure glaucoma (PACG) status post laser iridotomy in reversing the positive results of the dark room provocative test (DRPT).

- METHODS: This study was prospective, noncomparative, interventional case series. Thirty-three patients (thirty-eight eyes) with PAC or PACG status post patent laser iridotomy and maintained normal intraocular pressure (IOP) but with positive DRPT results were enrolled. All the subjects were treated with krypton LPIP. DRPT was repeated after krypton LPIP. Results of DRPT were recorded. The visual acuity, IOP and gonioscopy were analyzed before and after krypton LPIP. A minimum time limit for follow-up was 6 mo.

- RESULTS: Thirty-three patients (thirty-eight eyes) were followed for 17.7 ± 8.37 mo (range 7–41 mo) after LPIP. Positive results of DRPT decreased from 38 eyes to 9 eyes (23.7%) after LPIP. Peripheral anterior synechiae of angle in 34 of 38 eyes (89.5%) remained unchanged at dynamic gonioscopy throughout the follow-up period after LPIP.

- CONCLUSION: LPIP decreased positive rates of the DRPT significantly. The mechanism may be that LPIP minimized contact between the peripheral iris and trabecular meshwork, which is a key factor for developing peripheral anterior synechiae.

- KEYWORDS: iridoplasty; angle-closure glaucoma; laser

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INTRODUCTION

In China, glaucoma affects nearly 3% of the population aged 50 years or older. Primary angle-closure glaucoma (PACG) appears to be one of more severe disease [12]. The pathogenesis of primary angle closure (PAC) is uncertain, but evidences suggest that there are multiple mechanisms involved [13]. Previous studies showed that the majority of PACG in Chinese was caused by multiple mechanisms, such as the coexistence of both pupillary and non-pupillary blocking factors [8,9]. Laser iridotomy is a definitive treatment to relieve pupillary block in PAC and PACG [10,11]. However, peripheral anterior synechiæ (PAS) extension occurs in about 30% of eyes with PAC or PACG status post laser iridotomy [12,13]. Other studies also found the limitations of laser iridotomy in controlling intraocular pressure (IOP) in patients with PAC and PACG [14]. Iridotomy alone is not adequate as long-term therapy in eyes with PAC or PACG, and patients almost always require additional medical or surgical treatments[10]. The final common pathway for the development of angle-closure glaucoma, including those treated with patent laser iridotomy, is the contact between the iris and the trabecular meshwork especially in darkness. Thus, it produces the positive dark room provocative test (DRPT) result in angle closure. Laser peripheral iridoplasty (LPIP) is a means of opening an appositionally closed angle in situations in which laser iridotomy does not physically remove appositional contact because there are other mechanisms present, besides papillary block, which cannot be removed by laser iridotomy alone. The procedure consists of placing contraction burns in the extreme iris periphery to compact at the site of the burn, contract the iris stroma between the site of the burn and the angle, and physically pulling the angle open[15]. In 1977, Krasnov[15] first attempted to use this technique. Later, there were studies showing the
efficacy and safety of argon LPIP (ALPIP) in treating patients with chronic angle closure glaucoma, plateau iris syndrome, and acute attack of PAC. The means of evaluating the effect of LPIP on opening an appositionally closed angle include gonioscopy, ultrasound biomicroscopy (UBM), and IOP measurements. However, there have not been any prior studies that the DRPT used to observe the efficacy of LPIP. The DRPT had been used extensively in the past to identify subjects with narrow angles at risk for developing angle closure. Therefore, in this study we enrolled PAC and PACG patients, with patent post laser iridotomy status, who maintained a normal IOP but responded positively to DRPT to evaluate the efficacy of LPIP in reversing the DRPT result.

SUBJECTS AND METHODS

This study was a prospective, noncomparative, interventional case series. The subjects were consecutive patients with PAC or PACG status post patent laser peripheral iridotomy from February 2005 to April 2007 at the Glaucoma Service of Peking University Eye Center, Peking University Third Hospital. Ethical approval was obtained from the Institutional Review Board of Peking University Eye Center, Peking University Third Hospital. The study was conducted in adherence to the tenets of the World Medical Association's Declaration of Helsinki. All patients signed the documents of informed consent.

Inclusion criteria were: 1) subjects were patients with PAC or PACG; 2) patients had patent laser peripheral iridotomy; 3) IOP ≤21 mm Hg without medication; 4) positive DRPT results; 5) accept the LPIP therapy. DRPT was conducted in the following manner: IOP was first measured with Goldmann applanation tonometry; Each patient then sat on a chair without special position of the head for 1 h in a dark room; They were instructed to keep their eyes open and stayed awake during the test; At the end of the test, the patients were told to close their eyes wearing a black eyepatch and were taken as quickly as possible to the slit lamp where the IOP was remeasured. An increase in IOP of at least 8 mm Hg from baseline was considered a positive result for the test.

The exclusion criteria were: 1) patients with secondary angle closure resulting from iris neovascularization, uveitis, trauma, lens intumescence, or lens subluxation and with other mechanisms contributing to angle closure; 2) patients who could not be followed-up in our center; 3) patients who were not tolerant to the above examinations such as IOP, DRPT, gonioscopy and LPIP.

Demographic and ophthalmic data recorded in each case included age, gender, race, and data of presentation and onset of symptoms, anti-glaucoma drugs. Detailed ophthalmologic examinations included best-corrected visual acuity (Snellen visual acuity chart) and refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, Goldmann gonioscopy, ophthalmoscopy (especially recorded the vertical cup over disk ratio), visual field tested by Humphrey perimetry, SITA standard 30-2 program (Mk II, model 750, Zeiss-Humphrey, Dublin, CA, USA).

Slit-lamp gonioscopy was carried out by a single doctor (Wu LL) using a Goldmann-type 1-mirror lens at ×16 magnification with low ambient illumination. Care was taken to avoid light illuminating the pupil. Large movement was avoided in the static gonioscopy because of the possibility of indentation. Dynamic examination with increased illumination was carried out after static gonioscopy of all 4 quadrants to evaluate the presence of synechiae. Synechial closure was defined as angles where the entire trabecular meshwork was occluded by the iris and where the angle closure was not relieved by indentation. The examiner was masked to the previous gonioscopic results in each examination.

LPIP was performed on all eyes with topical anesthesia using a Goldmann gonioscopy (magnaview gionio laser lens, Ocular instruments inc. Bellevue, WA, USA) after administrating 3 drops of 1% pilocarpine. The laser used in this study was krypton green laser (Krypton ion laser, at 521-647 nm wave length. COHERENT, PALO ALTO, CA, USA). The laser was initially set at an energy level of 200 mW, then increased in 40 mW steps until adequate peripheral stromal contraction was noted. The duration of each laser pulse was 0.5 s, with a spot size of 500 μm. The laser beam was focused on the peripheral iris as close to the limbus as possible. The patients were asked to look in the same direction as the quadrant of iris being treated. All 4 quadrants (360°) were treated in the initial procedure. The treatment endpoint was a localized iris contraction at the treated site for each laser application. The laser energy level was reduced if any of the followings was observed: charring of the iris, release of pigment, formation of gas bubbles, or production of a "pop." sound, indicating a minute explosion. The laser energy level was increased if there was no contraction response from the iris. All the laser treatments were performed by the same doctor. The laser settings, including number of spots, power, spot size, wavelength, and duration of burn were recorded. IOP was measured one hour after LPIP. Patients were treated with topical corticosteroids 4 times daily for 2 wk.
Examinations on the follow-up visits included visual acuity, slit lamp examination, ophthalmoscopy, Goldmann applanation tonometer, and gonioscopy. The darkroom provocative tests were repeated four weeks after LPIP. Statistical analysis was carried out using the Statistical Package for Social Sciences version 13.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as the average± standard deviation. Parametric and nonparametric tests of significance were carried out where appropriate. Comparisons between groups were performed with Mann-Whitney U tests for continuous variables that were not distributed normally. Chi-square analysis was used for comparison of proportions, and the t-test was used for comparison of normally distributed continually variables. The exact P value was expressed for each comparison. A P<0.05 was considered significant.

RESULTS
In the two-year period, 568 eyes underwent the laser iridotomy procedure. Of the 568 eyes, 38 eyes (33 patients) that met the inclusion criteria were recruited in the study. All subjects were Chinese with brown iris (12 males and 21 females). Mean age of patients was 63.83±7.9y (range 45-76y). The mean follow-up time after LPIP was 17.7±8.37mo (range 7-41mo). The mean number of laser applications was 50.8±15.8 (range 14-69) and the mean energy level used in LPIP was 275.0±36.2 mW (range 240-440 mW).

Before LPIP, all eyes had patent laser iridotomy and maintained normal IOP without IOP-lowing medication but responded positively to the DRPT. The changes of IOP before and after the DRPT were shown in Figure 1. After LPIP, the DRPT produced negative results in 29 eyes (76.3%). Only 9 (23.7%) eyes still had positive DRPT result after LPIP. The results of DRPT after LPIP were shown in Figure 1. A comparison of the age, gender, range of PAS and laser treatment parameters between the 9 DRPT-positive and the 29 DRPT-negative patients were performed. However, no significant differences were found (all P>0.05).

The means of IOP before the LPIP treatment, one hour after LPIP, and at the final follow-up visit were 16.42±3.05 mm Hg (range 9.9-20.3 mm Hg), 19.40±5.96 mm Hg (range 10.7-35.4 mm Hg), and 16.40±3.40 mm Hg (range 10.9-24 mm Hg) respectively. There was no significant difference in IOP between the last follow up visit and before LPIP (τ=0.134, P=0.894; Figure 2). At one hour post-LPIP, IOP was significantly higher (τ=2.095, P=0.039). IOP's of 9 (23.7%) eyes were above 21 mm Hg and 2 (5.3%) eyes were above 30 mm Hg. For eyes with IOP>21 mm Hg, IOP before LPIP were significantly higher and the mean number of laser spots was significantly more than those with IOP ≤21 mm Hg. There were no statistically significant intergroup differences in the mean laser energy level and the extent of PAS (Table 1). After LPIP, gonioscopic findings showed increase in width of trabecular-iris angle and opening of appositionally closed angle in at least 1 quadrant in 38 eyes. The mean range of the PAS under dynamic gonioscopy before LPIP was

<table>
<thead>
<tr>
<th>Parameters</th>
<th>IOP pre-LPI (mm Hg)</th>
<th>Extent of PAS (clock hours)</th>
<th>Laser energy level (mW)</th>
<th>Laser spots (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with IOP &gt; 21 mm Hg 1h after LPIP (n=9)</td>
<td>18.37±2.67</td>
<td>3.42±3.72</td>
<td>281.6±32.8</td>
<td>59.23±14.76</td>
</tr>
<tr>
<td>Eyes with IOP ≤ 21 mm Hg 1h after LPIP (n=29)</td>
<td>15.64±2.95</td>
<td>3.53±3.21</td>
<td>272.4±37.6</td>
<td>49.43±13.03</td>
</tr>
<tr>
<td>P</td>
<td>0.001*</td>
<td>0.917</td>
<td>0.556</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

IOP: Intraocular pressure; PAS: Peripheral anterior synechiae; LPIP: Laser peripheral iridoplasty; *Significant.

Figure 1 Results of DRPT (dark room provocative test) before and after laser peripheral iridoplasty.

Figure 2 IOP (mm Hg) before laser peripheral iridoplasty and one hour, last follow up after laser peripheral iridoplasty *At one hour post-LPIP, IOP was significantly higher than IOP pre-LPIP.
2.57±2.97 clock hours (range, 0-6 clock hours), and 2.48±2.66 clock hours (range, 0-6 clock hours) at the final follow-up (P=0.724). PAS of angle in 34 of 38 (89.5%) eyes persisted under dynamic gonioscopy throughout the follow-up after LPIP. The remaining 4 eyes (10.5%) had progression of PAS during the follow-up period. Pigmentation of the angle was increased in all of the eyes. A mild postoperative iritis was the most common complication and responded well to topical steroid treatment, seldomly lasting more than a few days. Twelve (31.6%) patients experienced transient ocular irritation. Hemorrhage and cornea edema were not observed in any of the cases during the follow-up period. One (2.6%) patient had developed relatively widely dilated pupils post-laser. He suffered from mild photophobia for several days and recovered spontaneously. The pupil size normalized at the 6mo follow up.

**DISCUSSION**

In our study, all eyes had patent laser iridotomy and normal IOP but positive dark room test result before LPIP. After LPIP, however, the DRPT result changed negative in 29 eyes (76.3%). Previous studies showed that even with a patent surgical iridectomy or laser iridotomy, approximately 13%-40% of cases with PAC or PACG had a positive response to DRPTs [8,27]. For patients with PAC or early stage PACG, even with a patent laser iridotomy, IOP could be normal at diurnal hours, but it's easy to elevate at night or in the darkness. PACG patients with high IOP after LPIP are usually on glaucoma medications which affect the result of DRPT. Therefore, we only included those with normal IOPs without medications in our study; these represented angle occlusion and elevation of IOP possibly only at night, outside of working hours. The DRPT could provoke angle closure and IOP elevation. Although DRPT has low sensitivity [28], recent studies showed that IOP after DRPT was determined by the extent of functionally closed angle in darkroom test [26,29]. A negative provocative test does not exclude angle closure [28], but the significant difference in response to the provocative test between pre- and post- LPIP did demonstrate the efficacy of the treatment. This result implied that LPIP could effectively open appositionally closed angles.

The gonioscopy result in our study further suggested that LPIP indeed physically pulled open the angle and decreased the possibility of the appositional angle closure caused by the pupil dilation in darkness. Nine eyes (23.7%) still showed positive results of DRPT status post LPIP. There were no significant differences in the extent of PAS, laser treatment parameters between the 9 cases and the others. More cases are needed to study the mechanism of how LPIP reversing the DRPT result.

This study showed that the extent of the PAS under gonioscopy did not significantly increase in 89.5% of the eyes status post the LPIP treatment after mean follow-up time of 17.7mo. Mean IOP at the final follow-up was not different from that before LPIP. The extent of the PAS was similar to a previous result that the angle in 20 of 23 (87.0%) eyes remained open after one ALPIP treatment at mean follow-up of 6y [30]. Another study, in which the follow up duration was similar to ours, showed the rate of PAS progression was about 32.2% of eyes with PAC or PACG after iridotom y [12], which was much higher than 10.5% in our study. The difference implicated that LPIP was effective in preventing further development of PAS. Certainly, one must be careful about the gonioscopic evaluation of the angle in terms of grading the presence or extent of PAS. These parameters are highly variable and not necessarily objective for comparison within a study and across studies.

All subjects in our study were Chinese with brown iris, while the population in previous studies about LPIP were mostly Caucasians [20,30,31]. The use of argon laser, diode laser and double-frequency Nd:YAG laser in LPIP had also been described in the previous studies [17,32], but there was no report about the krypton laser in iridoplasty in recent years. From our experience, the mean laser energy setting and the mean number of burns of krypton for LPIP were similar to that of argon laser in previous studies [30].

The previous studies showed that LPIP was a safe procedure [12,30]. This study also showed no visual acuity significant change and other severe complication occurred after LPIP. IOP spike was considered to be one of the major complications [19]. However, up to this point, there was no related report and systematic analysis about the IOP spike after the LPIP. In order to observe the IOP spike, no IOP-lowing medication except pilocarpine was given before or immediately after LPIP in this study. Strict record showed that one hour after LPIP IOP was elevated mildly. IOP was elevated higher than 21 mm Hg in less than one fourth of eyes. Only 5.3% of the eyes had IOP higher than 30 mm Hg. The IOP elevation was related to the higher IOP level before LPIP and laser number of laser spots.

In this study we only enrolled the patients with normal IOP but with positive results of DRPT to observe the effect of LPIP in this test. Although we mentioned above that the different response to the DRPT before and after iridoplasty demonstrated the efficacy, the reliability of the test was still one of our main concerns as we all know the DRPT has high false negative rate and low sensitivity. We can take some measures, such as repeating the DRPT, in the future study to overcome this limitation. Another limitation was that this study did not have a control group. If the subjects with positive DRPT results are randomly allocated into two groups, one group could undergo krypton LPIP, the other group could serve as a control. The comparison of the positive rate of repeated DRPT results between the two groups would be more persuasive. Establishing the control...
group that showed the positive DRPT and had not undergone LPIP would give us more convincing results. And repeating the DRPT may decrease the uncertainty. Anyhow we should keep an eye on the subjects with negative provocative response and give right treatment strategy. Although PAS progression after LPIP was observed in only 10.5% eyes in our study but in the previous study 33% of eyes without LPIP treatment had PAS progression[2]. We can't be sure that the PAS will definitely further developed without intervention, and also whether the flattened peripheral iris may bow anteriorly again over time. Thus, we need a longer follow up.

In conclusion, in Chinese patients with PAC or PACG status post laser iridotomy, LPIP significantly decreases the frequency of positive response of DRPT; LPIP could be an effective method of opening appositionally closed angles when mechanisms other than pupillary block are present. Large sample studies with longer follow-up periods are needed to further investigate the therapeutic utility of LPIP in this clinical setting.

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Conflicts of Interest: Huang P, None; Wu LL, None.

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