Efficacy and safety of a new selective laser device to create anterior capsulotomies in cataract patients

Pavel Stodulka, MD, PhD, FEBOS-CR, Richard Packard, MD, FRCS, FRCOphth, David Mordaunt, PhD

**Purpose:** To compare the efficacy and safety of anterior capsulotomy creation with a new selective laser device (CAPSULaser) with those of manual capsulotomies.

**Setting:** GEMINI Eye Clinic, Zlin, Czech Republic.

**Design:** Prospective case series.

**Methods:** Patients were placed in cohorts based on age and cataract grade and randomly allocated to have laser capsulotomy or manual continuous curvilinear capsulorhexis (CCC). The anterior capsule was stained with microfiltered trypan blue 0.4%. The anterior capsulotomy was created with the laser device focused on the anterior capsule through a custom patient interface lens. Intraoperative video analysis with the use of an intraocular ruler and postoperative examinations were used to assess safety and efficacy (accuracy of capsulotomy size, circularity, centration).

**Results:** No intraoperative complications occurred in the laser group or the manual group. All capsulotomies in the laser group were free-floating with no tags or tears. The mean capsulotomy diameter was 5.03 mm overall (range 4.8 to 5.2 mm, laser group; 4.4 to 5.8 mm, manual group). In the laser group, all the capsulotomies were within 0.1 mm ± 0.1 (SD) of the target. The circularity accuracy was greater than 99.0% ± 1.0%; the mean centration of the capsulotomy in relation to the intracocular lens (IOL) was 0.1 ± 0.1 mm. All parameters were statistically significant (P < .01). The IOL-capsulotomy overlap was 360 degrees in all laser cases.

**Conclusions:** Selective laser capsulotomy using a new proprietary trypan blue formulation was safe and effective in cataract surgery. The sizing, circularity, and centration of the laser capsulotomy were more accurate than those of the manual CCC, resulting in consistent 360-degree IOL coverage.

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Zlin, Czech Republic. The protocol of the study was approved by the local ethics committee and the national regulatory authority (Czech State Institute for Drug Control). The clinical investigation began after all relevant ethics committee and regulatory authority approvals (study reference 16EL01) were obtained. Written informed consent was obtained from each patient according to the tenets of the Declaration of Helsinki.

Patients were placed into cohorts based on age and cataract grade and then randomly allocated to have a selective laser capsulotomy (laser group) or a CCC (manual group) using a stratified technique.12 Stratified randomization is a 2-stage procedure in which patients who enter a clinical trial are first grouped into strata according to clinical features that may influence outcome risk. Within each stratum, patients are then assigned to a treatment according to separate randomization schedules. The goal was to create homogeneous randomized populations for higher statistical accuracy for comparisons of potential surgical complications and non-inferiority.13

Inclusion criteria were a clinically documented diagnosis of grade I to IV cataract according to the Lens Opacities Classification System III,14 clear corneal media with no corneal disease or pathology that might interfere with passage of the laser light, age 40 to 79 years, and an endothelial cell count of more than 2000 cells/mm². To be included, patients must have read, understood, and signed the informed consent and agree to be randomized to either treatment group. Standard exclusion criteria were used and included previous eye surgery, ocular comorbidities, and poorly dilating pupils. The study protocol stipulated 4 investigational visits to ensure that the patients fulfilled the eligibility criteria.

### Selective Laser

The CAPSULaser unit attaches to the underside of the optics of a standard operating microscope using the mounting location for the Binocular Indirect Ophthalmomicroscope (BIOM, OCULUS Surgical, Inc.) (Figure 1). It is located so that the fixation light is coaxial with the ocular view of the surgeon.

The mechanism of action is selective laser absorption by a trypan blue–dyed anterior capsule. The wavelength of the laser is in the red–orange range of the spectrum and absorbs trypan blue applied to the anterior capsule. If the dye were not present, the laser light would pass through the capsule without interacting with it and rapidly extend to a large diffuse area on the retina. The dye absorbs the laser energy, providing localized heating of the capsule. This results in a phase change of the anterior collagen from type IV to amorphous. The laser is programmed to inscribe a circle; the collagen phase change allows the formation of a roll at the capsulotomy edge, which increases its elasticity, as shown by in vitro studies.17 Preclinical surgical testing on pig eyes and cadaver eyes combined with thermocouple measurements and histopathology have shown that selective laser capsulotomy has an excellent ocular safety profile.18 The laser is compliant with the relevant safety standards for use in ophthalmic surgery.19

### Preoperative Assessment

Preoperative examinations included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), automated and manifest refractions, anterior segment slitlamp evaluation, specular microscopy, intraocular pressure (IOP), optical biometry (IOLMaster, Carl Zeiss Meditec AG), fundus slitlamp evaluation, and optical coherence tomography.

### Surgical Technique

**Selective Laser Capsulotomy** A lid speculum was inserted and hydroxypropyl methylcellulose placed on the cornea. A paracentesis was created. Next, an air bubble was injected followed administration of a newly proprietary trypan blue formulation (CAPSULBlue, EXCEL-LENS, Inc.). The dye was left for 15 seconds and then washed out with a balanced salt solution. The chamber was filled with sodium hyaluronate 2.0% using a back-fill technique. Hydroxypropyl methylcellulose was again placed on the cornea, and the patient interface lens was positioned. The aiming beam of the laser was turned on and focused using the guide from the aiming beam. The fixation light was coaxial with the surgeon’s view, allowing most patients to fixate on the visual axis. Next the surgeon assessed centration and determined the location of the capsulotomy. The laser footprint was depressed, which activated the laser to fire with 1 continuous beam (versus multiple pulses) for 1 second to create the capsulotomy (Figure 2) (Video 1, available at http://jcrsjournal.org). The capsulotomy disk was removed with a forceps, and the remainder of the cataract

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laser</th>
<th>Manual</th>
</tr>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>61.8</td>
<td>62.2</td>
</tr>
<tr>
<td>Range</td>
<td>42, 79</td>
<td>42, 79</td>
</tr>
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</table>
surgery proceeded in typical fashion. All study-relevant laser settings were recorded.

**Continuous Curvilinear Capsulorhexis** A standard CCC was created using a forceps under an ophthalmic viscosurgical device. Once the disk was removed with the forceps, the remainder of the cataract surgery proceeded as normal.

**Postoperative Assessment**

Follow-up visits were performed at 1 week and 1 month and included the following: UDVA, CDVA, automated and manifest refractions, slitlamp evaluation, IOP, and fundus evaluation by optical coherence tomography. In addition, specular microscopy was repeated 1 month postoperatively.

Efficacy and safety were assessed based on video recordings during the surgery as well as postoperative examinations findings. Adverse events and all observations were documented in electronic case report forms. An external research organization performed site monitoring and controlled, verified, and analyzed the electronic case report forms. The full dataset was used for all reported results.

**Study Endpoints**

The following study endpoints were assessed: adverse events related to the treatment procedures, determined intraoperatively and 1 week and 1 month postoperatively; surgical efficacy of the new trypan blue formulation as an intraocular dye for staining the anterior capsule; efficacy of the selective laser in anterior capsulotomy creation; and assessment of mechanical attachments (tags or bridges) between the disk and the capsulotomy rim as well as anterior tears.

Other endpoints concerned efficacy and comprised the accuracy of the capsulotomy diameter size, circularity, and centration relative to the IOL. All measurable parameters and the analysis of these measurements were assessed by independent reviewers.

The accuracy of the capsulotomy diameter, defined as the absolute value of measured diameter subtracted from the intended target of 5.0 mm, was measured at the capsule plane using an intraocular ruler after the capsulotomy disk had been removed and before phacoemulsification. Videorecording frames that showed the capsulotomy edge and intraocular ruler were selected and analyzed for each capsulotomy. The image was calibrated with the ruler placed in the capsule plane during surgery. The capsulotomy rim edge was defined by the reviewer, who identified at least 40 points. The least-squares method was used to determine the best-fit circle (ie, circle diameter and center) for these identification points.

To be consistent with previous literature, circularity was assessed using 2 methods. First, it was calculated as follows: \( \frac{4\pi \times \text{area}}{\text{perimeter}^2} \). Second, the least-squares approach was used to determine the best-fit for an ellipse to the identified points, with the reported circularity value being the ratio of the major to minor axes. In both methods, a reading of 100% circularity represented a perfect circle.

A second video frame that clearly showed the capsulotomy edge and the outside diameter of the IOL optic was selected. The capsulotomy rim and the IOL perimeters were defined by the reviewer, who identified at least 40 points for each. This image was calibrated with the outside diameter of the IOL. The least-squares method was used to determine the best-fit circle for the capsulotomy and IOL outside diameter, determining that the best fit was the centration difference between the IOL and the capsulotomy.

**Statistical Analysis**

CONSORT guidelines were used to determine non-inferiority and superiority. Using SAS software (version 9.4, SAS Institute, Inc.), an outside biostatistician calculated a minimum sample size in each study group of 55 patients to achieve statistical confidence of at least 95% for non-inferiority, an assumed margin of non-inferiority of 0.05 mm, a test power of 0.8, and a dropout rate of less than 10%. If non-inferiority was determined for select laser capsulotomy, superiority was tested.

**RESULTS**

Three patients did not complete the study. Two patients failed to appear for postoperative visits in the study timeframe despite receiving reminders. One patient died from cardiac disease not related to the surgery. Table 1 shows the characteristics of the enrolled patients in the laser group and manual group. The sex and age of the patients was similar in the 2 groups.

**Table 2. Preoperative age range distribution by cataract grade and group.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>70–79</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>60–69</td>
<td>5</td>
<td>5</td>
<td>12</td>
<td>12</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>50–59</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40–49</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3. Preoperative and postoperative IOP by group.**

<table>
<thead>
<tr>
<th>Value</th>
<th>Laser Group</th>
<th>Manual Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop (n = 63)</td>
<td>Postop</td>
</tr>
<tr>
<td></td>
<td>1 Wk (n = 62)</td>
<td>1 Mo (n = 61)</td>
</tr>
<tr>
<td>Mean</td>
<td>16.3</td>
<td>15.1</td>
</tr>
<tr>
<td>SD</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Median</td>
<td>16.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Min</td>
<td>10.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Max</td>
<td>25.0</td>
<td>24.0</td>
</tr>
</tbody>
</table>
Table 2 shows the patient distribution by age range and cataract grade in both groups. The only between-group differences was the number of patients in the 40- to 49-year age range with grade I cataract; 1 of the patients in this category was not eligible based on the exclusion criteria and was removed from the study.

Safety
There were no capsulotomy or cataract surgery–related adverse events. No eye had flare, epithelial staining or erosion, abnormal iris changes, a malpositioned IOL, cystoid macular edema, or other abnormal signs.

Table 3 shows the preoperative and postoperative IOP; there were no significant differences in IOP values or the postoperative decrease in IOP between the laser group and the manual group. Statistical analysis of the change in IOP from preoperatively to 1-month postoperatively showed non-inferiority of selective laser capsulotomy compared with CCC, with a non-inferiority margin of 1.0 mm Hg ($P < .05$).

Efficacy
In the laser group, all anterior capsules were uniformly stained to an intense blue with a single application of the trypan blue. All capsulotomies in this group were free-floating with no mechanical attachments (tags or bridges) between the disk and the capsulotomy rim. No anterior or posterior tears occurred.

Capsulotomy Diameter
Figure 4 shows the difference in capsulotomy diameters between the laser group and the manual group. The means were close to the intended diameter of 5.0 mm in both groups. However, the precision of the distribution was greater in the laser group than in the manual group, with a standard deviation of 0.09 mm and 0.31 mm, respectively. The diameter was within ±0.1 mm of the target in 54 cases (86%) in the laser group and in 27 cases (44%) in the manual group. The capsulotomy diameter was within ±0.4 mm in the range from 4.8 to 5.2 mm in the laser group and within ±1.4 mm in the range from 4.4 to 5.8 mm in the manual group.

Figure 5 shows the frequency versus the diameter accuracy in both groups. The 99% confidence interval (CI) was 0.06 to 0.09 mm in the laser group and 0.17 to 0.30 mm in the manual group. Thus, the 99% CI for diameter accuracy was 30 μm and 130 μm, respectively. The complete CI in the laser group was more favorable than the mean in the manual group, showing that the diameter accuracy in the laser group was statistically significantly better (superior) than in manual group ($P < .01$).

Capsulotomy Circularity
Compared with the least-squares approach, the first method of calculating capsulotomy circularity ($4\pi \times \text{area}/\text{perimeter}^2$) was more sensitive.
to the smoothness of the edge and number of points used to identify the edge but was relatively insensitive to the overall capsulotomy shape. Both groups had a high degree of circularity (99.9% laser group; 98.5% manual group). The ratio of major axis to minor axis of the best-fit ellipse method was sensitive to the overall capsulotomy shape; thus, this ratio was used as the measure of circularity; the mean was 99.2% in the laser group and 98.1% in the manual group.

The distribution of circularity accuracy was close to the target in both groups (Figure 6). 55 cases (88%) in the laser group and 21 cases (34%) in the manual group were within 99% or more of circularity. The capsulotomy circularity accuracy (ratio of major to minor axes) in the laser group was 97% or better; the circularity accuracy in the manual group was 94% or better.

The 99% CI was 99.1% to 99.4% in the laser group and 97.7% to 98.4% in the manual group. The circularity accuracy in the laser group was statistically significantly better (superior) than in the manual group (P < .01).

Capsulotomy Centration

Figure 7 shows the capsulotomy centration relative to the IOL center. This could be measured only in approximately 50% of cases in the manual group because the pupil was smaller than the IOL optic and the IOL edge could not clearly be observed. Less miosis occurred and the pupils were more dilated in the laser group, and centration was measured in all patients. Centration of the capsulotomy was good in both groups, with all laser capsulotomies centered less than 0.15 mm from the IOL center. In 3 cases in the manual group, the capsulotomy was more than 0.4 mm from the IOL center, with the highest decentration being 0.78 mm. The laser and manual groups are characterized by a mean and 99% confidence interval of 0.06 ± 0.01 and 0.10 ± 0.07 mm, respectively. The centration accuracy in the laser group was statistically significantly better (superior) than in the manual group (P < .01).

Figure 8 (left) shows ideal centration on the pupil and IOL position, with complete 360-degree capsulotomy coverage of the IOL. In this case, the selective laser capsulotomy has a 5.0 mm diameter and 99.5% circularity and is decentered by 0.02 mm in relation to the IOL. Figure 8 (right) shows major misalignment of capsulotomy in regard to the pupil and IOL center, with incomplete 360-degree coverage. This example, an outlier in the manual group, is characterized by a 5.4 mm diameter, 97.2%, circularity, and 0.8 mm decentration from the IOL. The IOL is not in total alignment with the pupil center, as seen by the haptics that center the IOL on the capsule bag equator, which is not
In all cases in the laser group and 56 cases (91%) in the manual group, the capsulotomy edge covered the IOL for 360 degrees.

**DISCUSSION**

In recent years, technologies for creating more accurate capsulotomies than obtained with the CCC method have been developed; these include the use of femtosecond lasers and of precision pulse capsulotomy systems. The present clinical study determined that capsulotomy diameter, circularity, and centration were statistically more precise when selective laser capsulotomy was used than when manual CCC was performed. It also shows the value of homogeneous recruitment and randomized allocation in better balancing baseline variables between a study group and a control group.

The selective laser capsulotomy was safe, with no capsulotomy- or cataract surgery–related adverse events. All capsulotomies in the laser group were free floating with no mechanical attachments (tags or bridges) between the disk and capsulotomy rim. Furthermore, no anterior or posterior capsule tears occurred. Moreover, the clinical outcomes of the selective laser capsulotomy and CCC techniques were similar, with no statistically significant differences in the UDVA, CDVA, IOP, endothelial cell count, or related slitlamp and optical coherence tomography examination findings. We recognize that the best way to assess the endothelial cell count is in a contralateral study with at least 3 months of follow-up, and we are planning such a study.

The overall precision of the capsulotomy diameter size, circularity, and centration was significantly better in the laser group than in the manual group ($P < .01$). We saw a trend indicating that increased precision of these 3 factors would increase the rate of 360-degree coverage of the IOL by the capsulotomy. It has been shown clinically that incomplete 360-degree coverage of the IOL by the capsulotomy increases the likelihood of IOL tilting and malpositioning and the early-onset of posterior capsule opacification.

Nagy et al. reported incomplete IOL coverage in 11% of cases and 28% of cases in a femtosecond laser–assisted cataract surgery group and a CCC group, respectively. A 28% incomplete IOL coverage rate for CCC is high for modern uncomplicated cataract surgery. This implies a correlation between capsulotomy precision and 360-degree IOL coverage. It also suggests that a precise capsulotomy diameter is not the only factor and that accuracy in circularity and centration are also important to achieving complete 360-degree IOL coverage.

Good centration on the visual axis is especially critical in multifocal IOL and toric IOL implantation because small amounts of decentration and tilt degrade image quality. Well-centered capsulotomies and IOLs might also lead to better predictability of the effective lens position; however, this does not necessarily improve visual outcomes. Intraocular lens manufacturers are starting to produce IOLs that take advantage of accurately sized and circular capsulotomies for capsulotomy capture of the IOL optic. The precise centration of selective laser capsulotomies on the visual axis will be important with these emerging designs.

**Figure 7.** Deviation from centration by group. The horizontal lines with arrows represent the 99% confidence intervals.

**Figure 8.** Representative capsulotomies in laser group (left) and manual group (right). The gray dots represent the capsulotomy edge, and the blue circle represents the best fit of the dots. The green circle represents the outline of the IOL body, and the red circle denotes the pupil center.

**WHAT WAS KNOWN**

- Trypan blue can be used to stain the anterior capsule without adverse effects.
- Accurately sized capsulotomies covering the intraocular lens (IOL) edge lead to less posterior capsule opacification.
- Good centration is particularly important with advanced-technology IOLs.

**WHAT THIS PAPER ADDS**

- The use of a new trypan blue dye to stain the anterior capsule used in conjunction with a new laser for capsulotomies was safe and effective.
- The laser provided more accurate capsulotomy sizing, circularity, and centration than manually created continuous curvilinear capsulotomies.
In conclusion, this 125-patient clinical study found that selective laser capsulotomy and the new trypan blue formulation were safe and effective. No cataract surgery–related adverse events occurred. All laser capsulotomies were free floating, and no anterior or posterior tears occurred.

REFERENCES


OTHER CITED MATERIAL


Disclosures: Drs. Stodulka, Packard, and Mordaunt have a financial interest in the product CAPSULaser and are equity shareholders in EXCEL-LENS, Inc.