Comparative analysis of brilliant blue G and an intracameral illuminator in assisting visualization of the anterior capsule in eyes with vitreous hemorrhage

Young Min Park, MD, Jung Y. Park, MD, Jong Soo Lee, MD, PhD, Ji Eun Lee, MD, PhD, Ik Soo Byon, MD, Sung Who Park, MD

PURPOSE: To compare the safety and efficacy of 0.025 mg/mL brilliant blue G (BBG) and an intracameral illuminator for visualizing the anterior capsule.

SETTING: University-based tertiary referral center, South Korea.

DESIGN: Retrospective cases series.

METHODS: The medical records of patients with vitreous hemorrhage for which they had pars plana vitrectomy and cataract surgery were retrospectively reviewed. The patients were classified into 2 groups. The BBG group comprised patients having capsule staining with BBG. The illuminator group comprised patients who had capsulorhexis assisted with an intracameral illuminator. The status of the endothelial cells was analyzed.

RESULTS: There were 27 eyes in the BBG group and 35 eyes in the illuminator group. In the BBG group, endothelial cell density (ECD) was reduced 3 months after surgery (10.6% loss) ($P = .003$). The illuminator group had no significant loss (1.5% loss) ($P = .264$). The ECD loss was greater in the BBG group than the illuminator group 3 months after surgery ($P = .01$). There was no statistically significant difference in the coefficient of variation of cell area or percentage of hexagonal cells between the 2 groups.

CONCLUSIONS: The ECD loss was higher in eyes with 0.025 mg/mL BBG staining than in eyes using an intracameral illuminator. Further studies are necessary to establish the safety profile of BBG on the endothelium.

Financial Disclosure: None of the authors has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2016; 42:1015–1021 © 2016 ASCRS and ESCRS

Adequate continuous curvilinear capsulorhexis (CCC) is critical for ideal phacoemulsification, minimizing the risk for posterior capsule tear and ensuring stability of the intraocular lens (IOL).[1] However, creating a CCC is difficult in eyes without a sufficient red reflex. Thus, a few staining methods or assisted illumination devices have been used to visualize the anterior capsule during the CCC in such cases.[1–7]

In 2006, using animal models, Enaida et al.[8] and Hisatomi et al.[9] showed that 0.025 mg/mL brilliant blue G (BBG) (Sigma-Aldrich Co.) would be safe and useful to stain the anterior capsule or inner limiting membrane. Since then, there have been several studies showing BBG has been accepted as a safer dye than indocyanine green (ICG) or trypan blue for staining the inner limiting membrane.[9–12] However, since the animal study in 2006,[9] there has been no subsequent study investigating the use of BBG for visualizing the anterior capsule during cataract surgery.

The aim of this study was to evaluate the safety and usefulness of 0.025 mg/mL BBG for visualizing the anterior capsule.

PATIENTS AND METHODS

Patient Selection

This study was performed under the supervision of the Ethical Committee, Pusan National University Hospital, in accordance with the rules described in the Helsinki Declaration. This study was a retrospective analysis of the medical records of patients with vitreous hemorrhage for which they had combined pars plana vitrectomy, phacoemulsification, and IOL implantation. Informed consent was obtained from all patients before the surgery.

In eyes with insufficient red reflex, the CCC process was too difficult without additional support such as dyes or assistant illuminators. Because use of an intracameral illuminator is known to be a safe and effective method during the CCC process in patients with poor red reflex, a control group comprising patients who had CCC assisted with an intracameral illuminator was established. Patients were classified into 2 groups: the BBG group, in which patients had capsule staining with BBG during the CCC process, and the illuminator group, in which patients had CCC assisted with an intracameral illuminator. Preoperative cataract status was measured using a biomicroscope and graded using the 4 grading scales of the Lens Opacities Classification System III.[13]

The exclusion criteria were advanced age (>80 years), young age (<50 years), dense cataract (nuclear cataract grade >3), a history of ocular trauma or surgery, corneal disease, pseudoexfoliation syndrome, ocular inflammatory disease, a preoperative endothelial cell count less than 2000 cells/mm^2, glaucoma, and intraoperative or postoperative complications that required additional surgery within 3 months. Eyes with a major vascular arcade observed despite preoperative vitreous hemorrhage were also excluded.

Surgical Techniques

All surgeries were performed by the same surgeon (P.S.W.). Because vitrectomy is known to induce nuclear sclerotic cataracts, especially in patients older than 50 years,[13] cataract surgery was performed in every patient with consent. One hour before surgery, the pupils were dilated with tropicamide 0.5%, phenylephrine 0.5% (Tropherine), and cyclopentolate hydrochloride 1.0% (Ocucyclo), applied 5 times at 10-minute intervals. Retrobulbar anesthesia was administered in every case.

Brilliant Blue G Group Brilliant blue G was prepared according to a previously reported procedure on the day of surgery.[9] After limbal stab incisions were made, aqueous–air exchange was performed. Then, 0.025 mg/mL BBG was applied on the anterior lens capsule. The anterior chamber was thoroughly irrigated with a balanced salt solution immediately to wash out the BBG. After irrigation, the fluid in the anterior chamber was exchanged with hyaluronic acid 1.6%–chondroitin sulfate 4.0% (Discovisc). After a 2.8 mm superior clear corneal incision was created, CCC was made without assisted illumination.

Illuminator Group After limbal stab incisions were made, the aqueous was replaced with hyaluronic acid 1.6%–chondroitin sulfate 4.0% directly. After a 2.8 mm superior clear corneal incision was made, an intracameral endoilluminator was used without staining during CCC as previously reported.[6]

Both Groups Routine phacoemulsification, including nuclear fracturing (stop-and-chop technique), cortical cleanup, and implantation of a foldable 3-piece acrylic IOL (PC60AD, Hoya Corp.), was performed in both groups. Pars plana vitrectomy was performed using a Constellation sutureless 25-gauge vitrectomy system (Alcon Laboratories, Inc.) and a noncontact viewing system (Resight 700, Carl Zeiss Meditec AG).

Moxifloxacin 0.5% (Vigamox) and atropine 0.1% drops (Ocutropine) were instilled 4 times daily and dexamethasone 1.0% (Maxidex) 4 times daily for a maximum of 4 weeks postoperatively based on the degree of inflammation.

Clinical Data Collection and Corneal Endothelial Status Assessment

Preoperative and postoperative assessment included determination of corrected distance visual acuity (CDVA), slitlamp examination, intraocular pressure, and specular microscopy (KC-3309, Konan Medical) at baseline and 1 and 3 months after surgery. Intraoperative complications were also reviewed. Using computer-assisted photometric analysis, the central corneal endothelial cell density (ECD) (cells/mm^2), percentage of hexagonal cells, and coefficient of variation (CoV) of cell area were calculated. The number of endothelial cells at the center of the cornea was estimated in a mean area of 0.24 mm $\pm$ 0.4 (SD) on photomicrographs. For each eye, the mean value of each parameter that was measured in 3 photographs was calculated.

Statistical Analysis

Statistical analysis was performed with SPSS software (version 12.0, SPSS, Inc.). The Wilcoxon signed-rank test was used to determine significant changes after treatment. The Mann-Whitney *U* test was used to compare the results between the 2 groups. A *P* value less than 0.05 was considered statistically significant.

RESULTS

This study included 62 eyes of 62 patients; 27 eyes were assigned to the BBG group and 35 eyes to the illuminator group. Table 1 shows the baseline

Submitted: January 29, 2016.
Final revision submitted: March 28, 2016.
Accepted: March 30, 2016.

From the Departments of Ophthalmology, Gyeongsang National University School of Medicine (Y.M. Park), Gyeongsang National University Changwon Hospital, Changwon-si, Gyeongsangnam-do, School of Medicine (J.Y. Park, J.S. Lee, J.E. Lee, S.W. Park), Pusan National University and Medical Research Institute, Pusan National University Hospital, Pusan, and Pusan National University Yangsan Hospital (Byon), Yangsan, South Korea.

Corresponding author: Sung Who Park, MD, PhD, Department of Ophthalmology, School of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, 1-10 Ami-dong, Seo-gu, Pusan 602-739, South Korea. E-mail: oph97@naver.com.

Table 1. Comparison of baseline characteristics between the BBG group and the control group.

Parameter	BBG Group	Illuminator Group	*P* Value*
Eyes (n)	27	35	
Mean age (y) ± SD	56.9 ± 8.2	57.3 ± 9.7	.82
Male/female (n)	16/19	17/10	.21
Mean CDVA (logMAR) ± SD	1.93 ± 0.9	2.03 ± 0.8	.70
Mean IOP (mm Hg) ± SD	14.8 ± 2.4	14.2 ± 2.8	.43
Mean cataract grade ± SD	2.1 ± 1.2	2.0 ± 1.2	.85
Mean operation time (min) ± SD	56.6 ± 15.7	58.0 ± 14.4	.64
Underlying reason for vitreous hemorrhage (n)			
Age-related macular degeneration	3	2	.376
Branched retinal vein occlusion	6	8	.600
Diabetic retinopathy	16	18	.361
Retinal tear	2	7	.151
Underlying systemic disease (n)			
Diabetes mellitus	20	23	.583
Hypertension	14	12	.200

BBG = brilliant blue G; CDVA = corrected distance visual acuity; IOP = intraocular pressure
*Mann-Whitney *U* test; intergroup comparison

demographic characteristics in both groups; there were no statistically significant differences in any parameter.

The CDVA improved significantly after surgery compared with baseline in both groups. In the BBG group, the CDVA improved from 1.93 ± 0.9 logMAR at baseline to 0.59 ± 0.4 logMAR 1 month postoperatively and to 0.50 ± 0.5 logMAR 3 months postoperatively (both $P < .001$). The CDVA in the illuminator group improved from 2.03 ± 0.8 logMAR at baseline to 0.49 ± 0.6 logMAR 1 month postoperatively and 0.35 ± 0.5 3 months postoperatively (both $P < .001$).

The mean ECD in the BBG group decreased from 2742.4 cells/mm^2 before surgery to 2486.7 cells/mm^2 1 month postoperatively (9.3% loss; $P = .008$) and to 2452.6 cells/mm^2 3 months postoperatively (10.6% loss; $P = .003$). In contrast, compared with the preoperative level, the illuminator group had no significant ECD loss 1 month postoperatively (2.2% loss; $P = .174$) or 3 months postoperatively (1.5% loss; $P = .264$) (Figure 1). The ECD loss was greater in the BBG group than in the illuminator group ($P = .03$ at 1 month; $P = .01$ at 3 months). In 17 eyes (48.6%) in the illuminator group and 5 eyes (18.5%) in the BBG group, the preoperative ECD remained unchanged

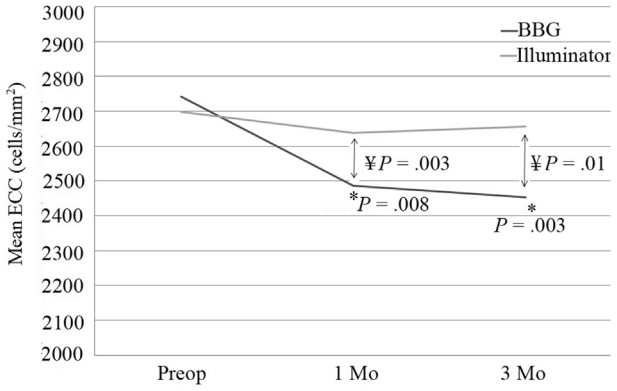

Figure 1. Mean endothelial cell count and postoperative endothelial cell loss (* = significant changes [$P < .05$] compared with preoperative values; ¥ = intergroup comparison [significant changes $P < .05$]; BBG = brilliant blue G; ECC = endothelial cell count).

until 3 months postoperatively (Figure 2), and there was a statistically significant difference between the groups ($P = .013$).

In both groups, the mean hexagonal cell count before surgery decreased significantly by 1 month postoperatively (6.8% loss, BBG group, $P = .007$; 5.1%, illuminator group, $P = .006$) and then recovered to preoperative levels by 3 months (4.5% loss, BBG group, $P = .160$; 1.4% gain, illuminator group, $P = .348$) (Figure 3). There was no statistically significant difference in postoperative hexagonal cells changes between the 2 groups.

In both groups, the mean baseline CoV remained unchanged until 3 months after surgery (Figure 4). There was no statistically significant difference in the postoperative CoV changes between the 2 groups.

In 3 of 62 eyes, the ECD decreased to less than 2000 cells/mm^2 in the postoperative period (Table 2). The 3 cases were in the BBG group. Except for the use of BBG, there were no common findings in baseline characteristics between these 3 eyes (Table 2). No eye had an ECD of less than 1000 cells/mm^2.

The BBG stained the anterior capsule homogenously, and the edge of the CCC could be clearly observed under the surgical microscope (Figure 5, *A*). In the intracameral illuminator group, the visibility of the anterior capsule was sufficient to perform phacoemulsification in every case (Figure 5, *B*). No eye evaluated in this study had CCC-related complications, such as a radial tear or posterior capsule rupture.

DISCUSSION

Because lens-sparing vitrectomy has a high risk for inducing postoperative cataract changes in old age,[13] vitrectomy combined with cataract surgery has become more common in cases of phakic eyes and in

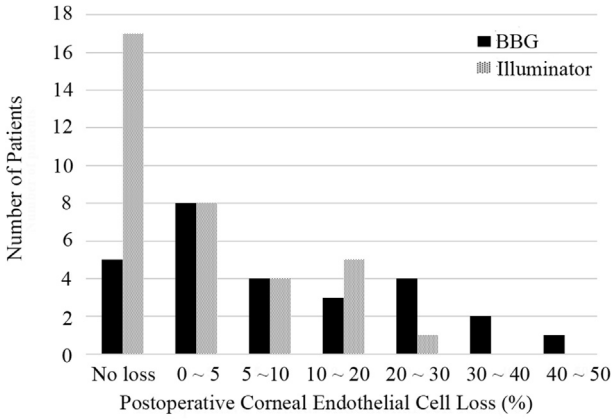

Figure 2. Loss of the ECD 3 months after surgery (BBG = brilliant blue G).

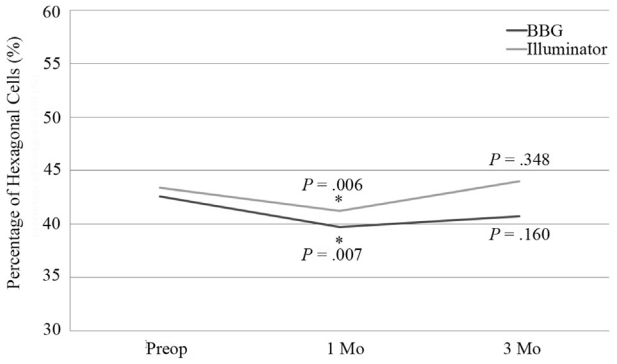

Figure 3. Mean percentage of hexagonal cells and postoperative changes in polymorphism (* = significant changes [$P < .05$] compared with preoperative values; BBG = brilliant blue G).

elderly patients. However, in cases with a poor red reflex, such as in eyes with vitreous hemorrhage, it is difficult to perform an adequate CCC, and this can result in an increased risk for intraoperative and postoperative complications. Additional steps to visualize the anterior capsule can be applied in such cases.

Brilliant blue G has been widely used for protein staining in the field of biology.[8] Diverse concentrations of BBG (10.0, 1.0, 0.1, 0.5, 0.25, 0.1, and 0.01 mg/mL) were first tried in the staining of intraocular structures in 2006.[9] The efficacy of BBG was evaluated using enucleated pig eyes; the conclusion was that a concentration of 0.025 mg/mL or higher could sufficiently stain the anterior capsule.[9] In addition, the safety of BBG has been evaluated in rat eyes and 0.025 mg/mL BBG has shown lower toxicity than 1.0 mg/mL trypan blue or 5 mg/mL ICG.[9] Brilliant blue G also showed no toxicity in the corneal endothelium or retinal cells at all concentrations when used to stain rat eyes.[8,9] The results in these previous studies[8,9] imply that a BBG concentration of 0.025 mg/mL can be used in human eyes.

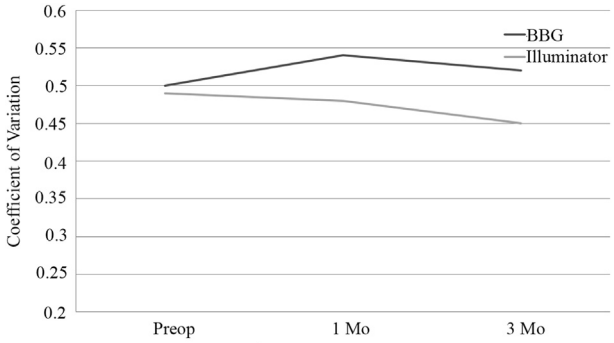

Figure 4. Mean value of the CoV and postoperative changes in polymegathism (BBG = brilliant blue G).

Previous studies of BBG focused only on its ability to stain the inner limiting membrane. After the use of 0.025 mg/mL BBG was evaluated in monkey eyes,[8] many clinical studies have been performed[10,11,14] and BBG has been widely accepted as a safer dye than trypan blue or ICG for staining the inner limiting membrane. Based on these results, BBG was produced commercially in the European Union in 2010 and marketed as ILM-Blue by the Dutch Ophthalmic Research Center, Zuidland, the Netherlands. ILM-Blue received orphan-drug designation by the United States Food and Drug Administration.[7] Because the safety and efficacy of 0.025 mg/mL BBG has been shown in earlier studies,[7–11,14] we expected that 0.025 mg/mL BBG could substitute for the conventional dyes trypan blue and ICG for staining the anterior capsule.

All cataract surgery can cause corneal endothelial cell damage.[15] The percentage of ECD loss after routine phacoemulsification has been widely reported as between 4.8% and 23.2%.[16–20] When compared with previous results,[16–20] a 10.6% postoperative ECD loss in the BBG group does not seem unusual. However, because the inclusion criteria in the current study differed from those in other studies, especially with respect to cataract density and combined with vitrectomy,[16–19] it is not reasonable to directly compare our results with those in other studies. Yamamoto et al.[20] found a 4.8% ECD loss after combined surgery using 0.06% trypan blue in eyes with vitreous hemorrhage; these data are the most comparable with those in our study.

In the illuminator group, there was no significant ECD loss (2.2%) after 3 months; therefore, the intracameral illuminator seems to be a safe method. On the other hand, a 10.6% loss of ECD in the BBG group could not be used to make a final conclusion with respect to safety. Comparison with other dyes is

Table 2. Three cases of postoperative ECD lower than 2000 cells/mm^2.

Case	Age (Y)	Underlying Disease	Group	Operation Time (Min)	Mean ECC (Cells/mm^2)		
					Preop	1 Mo	3 Mo
1	70	AMD	BBG	115	2288	1605	1704
2	61	BRVO	BBG	62	2577	1940	1302
3	57	DR	BBG	48	2309	1739	1761

AMD = age-related macular degeneration; BBG = brilliant blue G; BRVO = branch retinal vein occlusion; DR = diabetic retinopathy; ECC = endothelial cell count

essential to confirm or deny the safety of BBG. The additional surgical steps required for BBG staining, which include air injection, application of the BBG stain, and balanced salt solution irrigation, might have an effect on ECD loss. Further study will be needed to determine BBG toxicity to corneal endothelial cells. Although there was no significant reduction in ECD from 1 to 3 months postoperatively, the possibilities of ongoing ECD loss might have continued to occur after 3 months in the BBG group. The long-term safety of BBG on ECD should also be further evaluated.

Although ECD is mostly used to show the health status of the corneal endothelium, hexagonal cells and the CoV are sensitive indicators of corneal endothelial function.[21,22] In normal corneas, endothelial cells have 60% to 80% hexagonal cells. However, stress on endothelial cells can decrease hexagonal cells and thus increase pleomorphism.[21,22] The CoV is used as an index of the extent of variation in the cell area, which is referred to as polymegathism. Polymegathism is used as an indicator of permanent functional changes in the corneal endothelium.[23] In our study, hexagonal cells in both groups showed a significant reduction compared with the baseline at 1 month only. Because hexagonal cells in both groups recovered to preoperative levels 3 months after surgery, the temporary reduction in hexagonal cells might have resulted from acute stress induced by the surgery.

We believe that the present study is the first to assess the capsule-staining ability of 0.025 mg/mL BBG in humans. We found that the anterior capsule could be homogenously stained by BBG and that the capsule was clearly visible without sufficient red reflex. As mentioned, current data cannot be used to draw conclusions regarding the toxicity of 0.025 mg/mL BBG. Comparison with other dyes is required. In addition, these results are the first to evaluate the safety of the intracameral illuminator on corneal endothelial cells. Because there was insignificant ECD loss after the surgery in the intracameral illuminator group, the intracameral illuminator does not seem to cause significant damage to the corneal endothelial cells. Because all conventional dyes have been known to cause significant ECD loss postoperatively,[20,24] the insignificant postoperative ECD loss in the illuminator group is impressive. Moreover, as surgeons become more familiar with the use of secondary instruments during cataract surgery, using the intracameral illuminator during CCC might become more prevalent. The intracameral illuminator seems to be an easy and safe method in cases without a sufficient red reflex.

Because of the retrospective design of our study, surgical time was the only intraoperative parameter we were able to evaluate. Considering that we excluded eyes with high-density cataract, the intraoperative factors might not have significantly

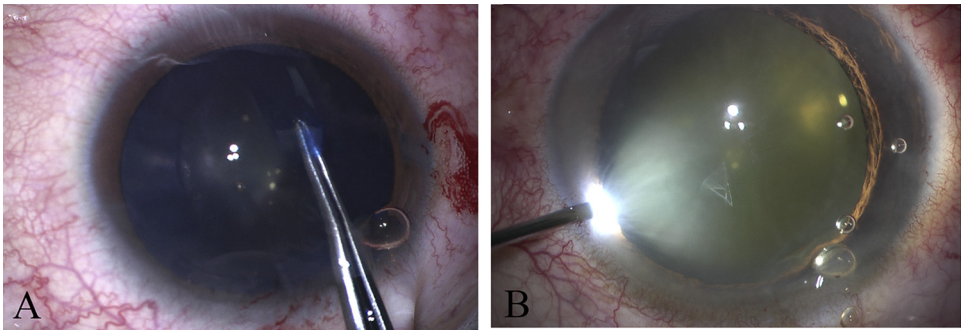

Figure 5. Continuous curvilinear capsulorhexis performed using BBG (*A*) and the intracameral illuminator (*B*).

biased our results. However, the lack of data on intraoperative factors, such as phacoemulsification time and energy, is the main limitation of our study. Follow-up studies should be prospectively designed, and more intraoperative factors should be considered.

For visualizing the anterior capsule in cases without sufficient red reflex, both 0.025 mg/mL BBG and the intracameral illuminator were efficacious. In terms of safety, the BBG group had higher ECD loss with the use of 0.025 mg/mL BBG than eyes in which surgery was performed using the illuminator. In conclusion, the use of an intracameral illuminator would appear to be a safe method, although further studies are necessary to determine the safety profile of BBG staining.

WHAT WAS KNOWN

- In eyes with insufficient red reflex, the CCC process is too difficult without additional support, such as dyes or illuminators.
- Results in studies using animal models suggest that 0.025 mg/mL BBG is safe and useful for staining the anterior capsule.

WHAT THIS PAPER ADDS

- For visualizing the anterior capsule in cases without sufficient red reflex, both 0.025 mg/mL BBG and the intracameral illuminator were efficacious.
- In terms of safety, use of the intracameral illuminator seemed to be a safe method, although further studies are needed to determine the safety profile of BBG staining.

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First author:
Young Min Park, MD

Department of Ophthalmology, Gyeongsang National University School of Medicine, Gyeongsang National University Changwon Hospital, Changwon-si, Gyeongsangnamdo, South Korea