Accidental Subretinal Brilliant Blue G Migration During Internal Limiting Membrane Peeling Surgery

Felipe P. P. Almeida, PhD, MD; Ana Claudia De Lucca, PhD, MD; Ingrid Ursula Scott, MPH, MD; Rodrigo Jorge, PhD, MD; Andre Messias, PhD, MD

Brilliant blue G (BBG) selectively stains the internal limiting membrane (ILM), improving visualization during ILM peeling.1 Despite controversy about the safety profile of the dye, BBG has been widely used intraoperatively in many countries.1 Accidental delivery of dyes into the subretinal space is a well-known complication associated with macular surgical procedures.2-5 In this report, we describe the outcomes of retinal function and structure during 2 years in a patient after epiretinal membrane (ERM) and ILM peeling with accidental migration of BBG into the subretinal space at the macular area.

Report of a Case

A man in his 60s presented with decreased visual acuity and progressive metamorphopsia for 6 months in his right eye. The patient had a history of glaucoma and had been monitored in our clinic for the past 5 years with well-controlled intraocular pressure and stable visual field defects.

Examination demonstrated a best-corrected visual acuity (BCVA) of 20/70 OD and 20/20 OS. Intraocular pressure was 13 mm Hg and 12 mm Hg, respectively. Slitlamp examination demonstrated mild nuclear sclerosis in each eye. Dilated ophthalmoscopic examination demonstrated thinning of the neuroretinal rim in each eye and an ERM with vascular tortuosity in the right eye. Optical coherence tomography (Heidelberg retinal angiography; Heidelberg Engineering) of the right eye was notable for an ERM and a central subfield macular thickness (CSMT) of 596 μm (Figure 1). Multifocal electroretinography (mfERG) (Espion E2; Diagnosys LLC) of the right eye revealed normal amplitude and implicit times before surgery but decreased amplitudes and increased implicit times in at least 5 contiguous hexagons after surgery on all 3 examinations performed during the 2-year follow-up period. These functional changes were not topographically correlated with the area of fluorescein staining or with the internal limiting membrane peeled area, but were matched to the area where brilliant blue G accidentally entered the subretinal space. Microperimetry demonstrated reduced retinal threshold sensitivity, particularly in areas with decreased multifocal electroretinography amplitude.

CONCLUSIONS AND RELEVANCE Despite the visual acuity improvement observed in this case, multifocal electroretinography and microperimetry indicate that subretinal brilliant blue G might cause focal macular damage with a decrease of macular function suggestive of a toxic effect.

Video at jamaophthalmology.com

Author Affiliations: Department of Ophthalmology, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil (Almeida, De Lucca, Jorge, Messias); Department of Ophthalmology, Penn State College of Medicine, Hershey, Pennsylvania (Scott); Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania (Scott).

Corresponding Author: Felipe P. P. Almeida, PhD, MD, Department of Ophthalmology, Ribeirão Preto School of Medicine, University of São Paulo, Avenida Bandeirantes 3900, Ribeirão Preto-SP, 14049-900, Brazil.
vitreous and facilitate posterior hyaloid detachment. The ERM was removed with a macular forceps.

With the infusion line closed, a solution of BBG, 0.05% (Ophthalmos), 280 mOsm (0.3 mL in a 5-mL syringe), was injected through a 23-gauge soft-tip silicone cannula into the vitreous cavity directed toward the optic nerve. An accidental BBG flush was noted during the infusion, presumably due to excessive pressure.

After the BBG was removed from the vitreous cavity, subretinal BBG was visualized in the macula despite the absence of retinal breaks (Figure 3A and Video). The ILM was peeled, and no internal drainage of the subretinal BBG was performed. Fluid-air exchange was conducted (approximately 25 mm Hg) just before the operation was completed.

**Postoperative Evaluations**

A blue area corresponding to the submacular BBG was visualized on the first postoperative day but was no longer visible 7 days later. The patient's BCVA, metamorphopsia, and CSMT improved progressively. At 3 months postoperatively, his BCVA was 20/50 and optical coherence tomography demonstrated some cystoid macular edema with a CSMT of 431 μm. At 5 months postoperatively, the BCVA had decreased to 20/80 and optical coherence tomography demonstrated increased cystoid macular edema with a CSMT of 533 μm. Therefore, an intravitreal injection of triamcinolone acetonide, 1 mg, was administered and was associated with an improvement in BCVA (20/25 at 1 year) and CSMT, which remained stable throughout 2 years of follow-up (Figure 1).

Fluorescein angiography was performed at 1, 3, 6, 12, and 24 months after surgery. Figure 3C shows postoperative fluorescein angiography that revealed no leakage around the optic nerve area (no sign of edema) and macula staining, probably due to a window defect in consequence of retinal pigment epithelium atrophy. The area of staining was smaller than the area where the ERM had been located, smaller than the area of ILM peeling, and smaller than the area where the subretinal BBG had been visualized (Figure 3D).

Multifocal electroretinography demonstrated amplitude and implicit times within the reference range before surgery, but an amplitude reduction was observed postoperatively in the retinal area between the fovea and the optic disc up to the 12-month postoperative visit. In addition, a predominantly central mfERG amplitude reduction was observed 24 months postoperatively. There was a region in which the mfERG responses showed reduced amplitude and increased implicit time (>20%) in at least 5 contiguous hexagons compared with preoperative values at postoperative month 1; these abnormal mfERG responses remained stable from postoperative month 1 through postoperative month 12 (Figure 2). At postoperative month 24, an overall improvement in mfERG responses was observed, probably owing to reorganization of the inner retina, although the central amplitude density (P1 amplitude in nanovolts per degree2 divided by the correspondent stimulus hexagon area) remained reduced.

**Discussion**

It is well established that removal of the ILM during ERM surgery helps to decrease ERM recurrence and that ERM and ILM can be peeled more easily if stained with dyes such as triamcinolone acetonide, trypan blue, or BBG. This report describes accidental subretinal BBG entry, presumably through an unobserved retinal hole induced by the dye jet stream that we believe was at the temporal edge of the optic disc. Postoperatively, our patient developed cystoid macular edema, which was treated with a single intravitreal injection of triamcinolone acetonide, with subsequent improvement in his BCVA and CMST. Nevertheless, we found functional and structural retinal abnormalities during follow-up, including staining on fluorescein angiography and reduced amplitudes and increased implicit times in the macula on mfERG.
There are previous reports of changes shown on fluorescein angiography and optical coherence tomography (window defects and outer retina damage) in the areas of the retina exposed to subretinal BBG, but there is no definitive evidence that these findings were due to the dye. It is also known that mfERG abnormalities may be present in eyes with ERM and that a further amplitude reduction may be observed in the peeled areas after surgery, even without the use of intraoperative dyes. For instance, Tari et al suggested 2 potential reasons for mfERG amplitude reduction after ILM peeling: (1) the presence of retinal cellular structures on peeled ILM samples, including Müller cell footplate processes, and (2) other retinal structural abnormalities denoted by the residual increased retinal thickness even after successful surgery, suggesting residual edema.

Figure 2. Multifocal Electoretinography (mfERG)

A. The mfERG stimuli scale with the threshold sensitivity in decibels. The range is calculated among the minimum and the maximum intensity level of the projected stimuli. B. The mfERG trace arrays. C. Topographic (3-dimensional) response density plots. Green represents normal values; yellow, suspect; red, abnormal; and black, scotoma. N indicates nasal retina; nV/deg², nanovolts/degree²; and T, temporal retina.

Figure 3. Fundus, Multifocal Electoretinography (mfERG), and Microperimetry

A. Intraoperative snapshot. B. Microperimetry at 24 months. C. Postoperative mfERG overlaying angiogram. Late phase (5 minutes) of a fluorescein angiogram demonstrates staining in the central macula overlaid by the mfERG responses. D. Near-infrared microperimetry at 24 months. The area highlighted in pink represents the area of the internal limiting membrane (ILM) peeled retinal region. The area highlighted in blue represents the area where mfERG responses showed reduced amplitude and increased latency. There was no correspondence between the areas with staining and the areas of mfERG abnormalities.
We found focal mfERG changes (decreased amplitudes and increased implicit times) after ILM peeling surgery in all 4 mfERG examinations performed during the 2-year postoperative period. These changes were not topographically correlated with the area of fluorescein staining or to the peeled area, but they were correlated with the area where BBG accidentally entered the subretinal space (Figure 3). Unfortunately, microperimetry results were available only for the 24-month postoperative visit, but the results indicated good topographic correspondence between areas of mfERG amplitude reduction and retinal threshold sensitivity.

The visual acuity improvement to 20/25 provides evidence against a toxic process involving the fovea, which could be explained if the dye did not reach the foveal area, which apparently is what happened in our patient.

Conclusions
Accidental subretinal migration of BBG, 0.05%, may cause cystoid macular edema and a persistent decrease of retinal function owing to a direct mechanical and/or toxic effect on retinal tissue. Studies are warranted to confirm such observations, and the development of safer intraoperative delivery method of dyes during chromovitrectomy is advisable.