New Application of Membrane Blue-Dual Dye for Retinal or Iatrogenic Break Staining

E. Papavasileiou

Evangelia Papavasileiou
MD, PhD, FEBOphth is
a Vitreoretinal Consultant

ABSTRACT

Chromovitrectomy is a novel approach to visualise the vitreous or retinal surface during vitreoretinal surgery and was motivated by the difficulty in visualising several thin and transparent tissues at the vitreoretinal interface such as the internal limiting membrane (ILM), epiretinal membrane (ERM) or vitreous, particularly the posterior hyaloid membrane. Numerous vital dyes with high specific affinity for the ILM have been applied in ILM peeling such as indocyanine green (ICG) and trypan blue (TB). Our results suggest that intravitreal injection of Dual Blue dye is a simple, safe and effective technique that can facilitate the identification of clinically undetectable retinal breaks in patients with primary retinal detachment and can result in high primary reattachment rate at 6 months follow up (in our case series we had 100% success rate). The use of intravitreal Dual Blue dye can be one additional option in vitreoretinal surgeons' armamentarium of surgical techniques dealing with unidentified retinal breaks.

Key words: Chromovitrectomy, undetected retinal breaks, retinal break staining.

General Hospital 'O AGIOS DIMITRIOS' of Thessaloniki Greece

Corresponding author: E. Papavasileiou
e-mail: liapapava@hotmail.com

In 1932, Lobeck[1] and coworkers were the first to perform intravitreal injection of vital dyes; a pioneer report has been released by Abrams et al.[2] demonstrating the first intraoperative use of vital dye, with fluorescein as a good adjuvant for vitreous identification. Since 2000 the application of dyes to stain preretinal tissues during vitreoretinal surgery has become a widespread technique among vitreoretinal surgeons.

Numerous vital dyes with high specific affinity for the ILM have been applied in ILM peeling such as indocyanine green (ICG) and trypan blue (TB). Intravitreal injection of ICG facilitated the visualization of ILM[3]. However, the use of indocyanine green (ICG) has been associated with adverse effects such as visual field defects, reduced visual acuity, and persistent staining[4] which may be aggravated by low osmolarity, bright endoillumination, and use of concentrations greater than 0.05 mg/mL.[5] Later, TB was proposed as a helpful tool to identify epiretinal membranes, and intravitreal triamcinolone acetonide (TA) was found to stain the vitreous[6]. A few other dyes including infracyanine green, patent blue, bromophenol blue, brilliant blue (BBG), and sodium fluorescein have been proposed as alternative dyes during chromovitrectomy[7,8].

Recently, extensive laboratory studies have yielded two novel commercially available and CE-approved dye solutions, **MembraneBlue-Dual™** and **ILM-Blue™**, that may have a higher efficacy as a result of the synergistic effect through the use of two dyes within the same sample, combined with polyethylene glycol (PEG) to increase the molecular weight and viscosity. MembraneBlue Dual® tissue dye is a sterile, non-inflammatory solution of Trypan Blue and Brilliant Blue G, dissolved in a physiological sodium chloride phosphate buffer with 4% Polyetheylene Glykol.[9,10,11]

Future studies may explore the use of fluorophore-labeled antibodies directed against specific macular tissue which, if combined with selective illumination and barrier filters, may lead to highly specific fluorescent staining of ocular tissues.[12]

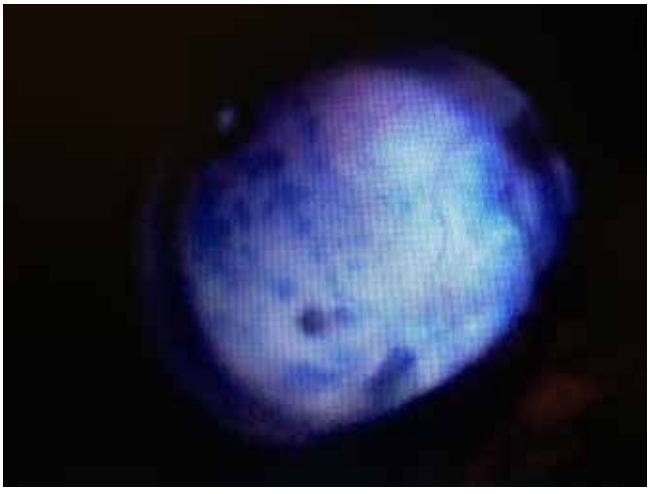
Each ml MembraneBlue Dual® contains (±5%):[9]

0.25 mg Brilliant Blue G purified
1.5 mg Trypan Blue, Purified
40 mg Polyethylene Glycol 3350
1.9 mg disodium hydrogen phosphate dihydrate
0.3 mg sodium dihydrogen phosphate dihydrate
8.2 mg sodium chloride
Balance to 1ml: water for injection

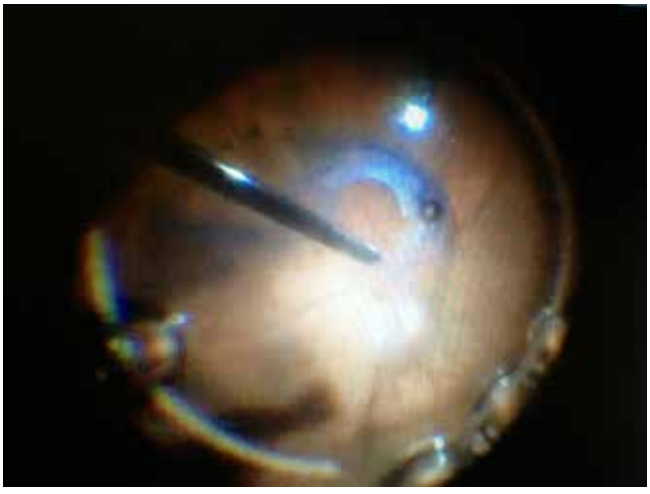
Advantages of Dual Blue dye:

1. stains both ERM and ILM (double stain as with Brilliant Blue) to facilitate peeling

2. improves intraoperative visualisation of membranes of interest and helps the discrimination of these membranes from surrounding intraocular structures as it yields enhanced



Picture 1. Patchy staining of the posterior hyaloid membrane with Dual Blue.



Picture 2. Posterior vitreous detachment with a 23-gauge cutter assisted with Dual Blue staining.

Picture 3. The intravitreal Dual Blue dye penetrated the peripheral detached subretinal space through the retinal break.

color-staining contrast against the orange-red attached retina or the whitish detached retina

3. can be injected in a BSS filled vitreous cavity (no need for additional air exchange as with membrane blue)

4. stains the posterior hyaloid membrane which can then be grasped and elevated with the vitrectomy cutter (Pictures 1 and 2)

5. Has minimal toxicity or safety concerns

Properties of Dual Blue:

1. sinks immediately as a cohesive ball to the posterior pole and provides a viscous and dense solution

2. only stains the targeted tissue

3. can be also diffuse throughout the whole globe and stain the peripheral ILM (indented dispersion) [9]

Staining the ILM or epiretinal membranes allows surgeons to work more quickly and precisely, thereby potentially improving surgical safety and anatomical outcomes. There are four main target tissues for staining during chromovitrectomy. Vital dyes such as TB exhibit outstanding affinity for ERMs because of the strong presence of dead glial cells within those membranes. ILM staining with TB is subtler than with ICG, and possibly TB stains the fine ERM overlying the ILM rather than the ILM itself. The usefulness of TA to highlight the vitreous has also been proposed. TA enables the visualisation of both prolapsed vitreous to the anterior chamber or posterior vitreous remaining in the vitreous cavity.

The principles of surgery for managing primary rhegmatogenous retinal detachment (RRD) are to precisely identify and treat all causative retinal breaks. Breaks responsible for RRDs may not be seen preoperatively owing to opacities in the media, pseudophakia, poor dilation or other causes. Estimates regarding unidentified breaks complicating RRDs vary from 2.2-22.5%[13-15]

Various strategies have been used to identify and manage primary retinal breaks intraoperatively when they have not been found before surgery, including circumferential buckling, broad retinopexy, scleral buckling, and pars plana vitrectomy (PPV)[16-21]. When retinal breaks can be identified intraoperatively, primary reattachment rates are significantly higher than when retinal breaks cannot be identified before or during surgery[16-21].

During recent years, advances in the PPV technique have allowed the surgeon to conduct a detailed intraoperative examination of the peripheral retina and, thereby, identify small retinal breaks. A new application for dyes in chomovitrectomy consists of staining retinal break edges during vitrectomy for rhegmatogenous retinal detachment repair was suggested in 2007. Jackson et al.[22] demonstrated the success of this technique to identify retinal breaks in 4 out of 5 patients and concluded TB-guided retinal break detection to be a very useful surgical technique. In this technique, TB 0.15% is injected transretinally into the subretinal space using a 41-gauge cannula.

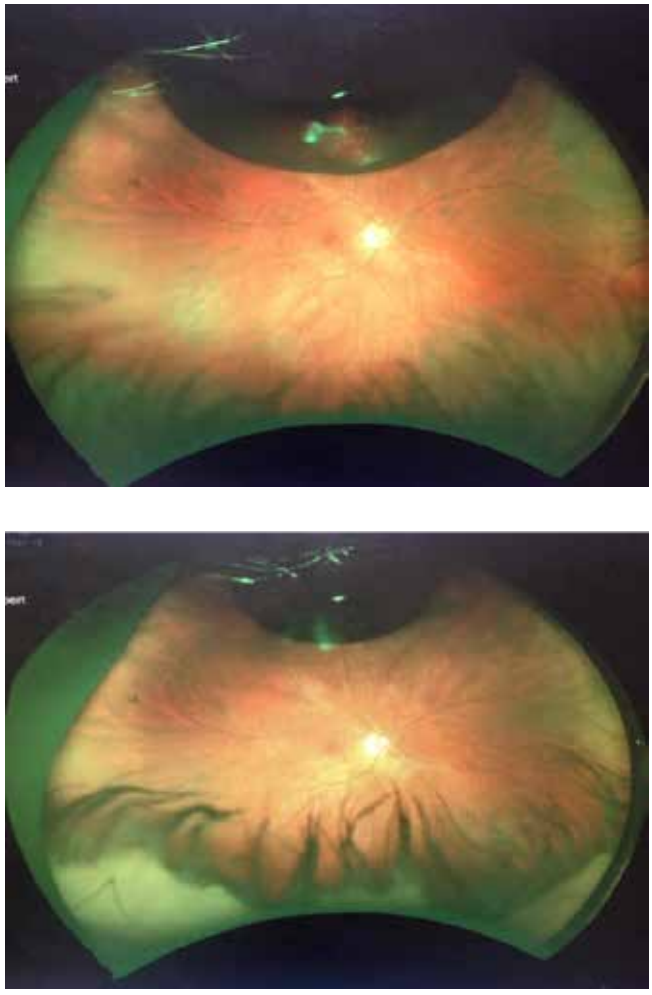
In order to evaluate the efficacy of MembraneBlue-Dual heavy dye solution for staining of retinal and iatrogenic breaks we performed a prospective non-randomized interventional study using the high molecular weight dye MembraneBlue-Dual (0.15% trypan blue, 0.025% brilliant blueG, 4% PEG) in 23 gauge vitrectomy surgeries for primary repair of 10 patients with rhegmatogenous retinal detachment (RRD) where no breaks where identified prior to surgery despite meticulous pre-operative examination using binocular indirect ophthalmoscopy with indentation. In all cases MembraneBlue-Dual enhanced staining, thus facilitating the identification of undetectable retinal or iatrogenic breaks. None of the surgeries required the use of perfluorocarbon heavy liquid, fluid-air exchange to assist the dye application,

or subretinal injection of dye. Subretinal fluid was stained which enabled surgeons to identify and drain through the break (Picture 3). A drainage retinotomy was not required in any patient. No retinal adverse effects related to the surgery or use of the dye were observed based on serial autofluorescence images up to 6 months after surgery.

Vitrectomy surgeries were performed during which a posterior vitreous detachment was created. The surgeons performed all scleral depression using a muscle hook which was started at the most probable location of the retinal break and then continued along the entire retinal periphery. Without performing a prior fluid-air exchange 0.1 ml of Membrane-Blue-Dual™ was applied into the vitreous cavity, while it was completely filled with fluid, and all excess dye was aspirated with a blunt backflush instrument. In all cases, the intention was to identify peripheral PVD-related retinal or iatrogenic breaks and to treat them with cryotherapy or endolaser. A retinal break was defined as primary when it was judged from the contour of the detachment that this break alone could account for the detachment. A break was defined as secondary when the contour of the detachment could not be accounted for by this break alone. In one case a parafoveal iatrogenic break was identified close to the area where macular ERM peeling was performed. In all eyes with RRD, the surgery was completed by gas tamponade (C2F6, C3F8 or SF6). After absorption of the gas tamponade all retinas remained attached. We compared the number of breaks identified when examined intraoperative with internal peripheral indentation before and after injection of the dye and found that in all cases (100%) at least one more break was found after injection of dye which was subsequently treated with cryotherapy or endolaser. At last follow up six months after surgery the success rate was 100% and none of them re-detached. (Picture 4 a, b).

DISCUSSION

A number of management techniques and strategies are available for treating retinal detachments in which the breaks are undetected pre-operatively. An internal search for retinal breaks using deep kinetic indentation of the sclera with combined endoillumination was first described by McLeod, using PPV and enables identification of retinal breaks in 95% of RRD cases.[23] This has been further elaborated to a dye extrusion technique,[22, 24] involving injection of sub retinal trypan blue, using a 41-gauge needle, into the SRF. Extrusion of the dye is encouraged through the presumed break using perfluorocarbon liquid to fill the eye and systematic rotation of the globe, with the aim of seeing a plume of dye venting out of the break. The use of a dye provides color contrast that aids detection and is an advantage over the use of heavy liquid alone. In some instances, the dye stains the devitalized tissue of the break itself. This was reported in the context of both primary and repeat RD repair.[22,24] In small size retinal breaks there is small amount of subretinal fluid streaming out through the breaks even after the use of PFO thus, the



Picture 4 a, b. Serial color photos with Optos in a patient with RRD. The retina remained attached after absorption of the gas tamponade.

Schlieren effect is difficult to identify. 18 Both these techniques carry the potential risk of retinal toxicity, especially as some dye may be left in the subretinal space.

Gupta D et al.[25] published a case series where Vision Blue (0.006% version of Trypan Blue) has been injected trans-sclerally into the subretinal fluid under the detached retina to identify clinically undetected (occult) retinal breaks in the setting of retinal re-detachments. This technique offers the advantage that iatrogenic break creation is avoided compared to trans-retinal injection. However, after injection of dye an air exchange is required to encourage the dye posteriorly. Theoretically, possible complications of this technique include hypotony, choroidal haemorrhage, retinal haemorrhage and retinal and vitreous incarceration.[26] Wu et al.[27] suggested the use of scleral buckling that extended over the circumference of the RRD with cryotherapy in the initial treatment of pseudophakic RRD with undetected retinal breaks with 72% anatomic success increased to a higher overall success rate after PPV with long-term tamponade for recurrent RD after primary buckling. Martinez-Castillo V et al.[28] reported 98% and 100% primary and final success rate respectively using pars plana vitrectomy alone with diffuse illumination and extensive vitreous dissection in order to identify and manage retinal breaks undetectable before surgery.

CONCLUSION

The greatest advantage of use of this dye solution MembraneBlue-Dual is improved intraoperative identification of ILM at the edges of retinal breaks and the discrimination of them from surrounding intraocular structures. Due to its increased molecular weight and viscosity properties it eliminates the need for fluid-air exchange or subretinal injection. The better the ILM can be identified the lower the chance that further surgery due to undetectable retinal or iatrogenic breaks will be needed.

Our results suggest that intravitreal injection of Dual Blue dye is a simple, safe and effective technique that can facilitate the identification of clinically undetectable retinal breaks in patients with primary retinal detachment and can result in high primary reattachment rate at 6 months follow up (in our case series we had 100% success rate). The use of intravitreal Dual Blue dye can be one additional option in vitreoretinal surgeons' armamentarium of surgical techniques dealing with unidentified retinal breaks.

REFERENCES

1. Lobeck E. Untersuchungen Über die Bedeutung des Netzhautrisses bei Netzhautablosung. Experimentelle Untersuchungen Über den intraocularen Flussigkeitswechsel bei künstlicher Netzhautablosung. Albrecht Von Graefes Arch Ophthalmol 1932; 128:513-573.

2. Abrams GW, Topping T, Machemer R. An improved method for practice vitrectomy. Arch Ophthalmol 1978; 96(3):521-525.

3. Rodrigues EB, Meyer CH, Farah ME, Kroll P. Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes. Ophthalmologica 2005; 219(5):251-256.

4. Stanescu-Segall D, Jackson TL. Vital staining with indocyanine green: a review of the clinical and experimental studies relating to safety. Eye 2009; 23(3):504-518.

5. Jackson TL, Hillenkamp J, Knight BC, et al. Safety testing of indocyanine green and trypan blue using retinal pigment epithelium and glial cell cultures. Invest Ophthalmol Vis Sci 2004; 45(8):2778-2785.

6. Li K, Wong D, Hiscott P, Stanga P, Groenewald C, McGalliard J. Trypan blue staining of internal limiting membrane and epiretinal membrane during vitrectomy: visual results and histopathological findings. Br J Ophthalmol 2003; 87(2):216-219.

7. Rodrigues EB, Maia M, Meyer CH, Penha FM, Dib E, Farah ME. Vital dyes for chromovitrectomy. Curr Opin Ophthalmol 2007; 18(3):179-187.

8. Morales MC, Freire V, Asumendi A, et al. Comparative effects of six intraocular vital dyes on retinal pigment epithelial cells. Invest Ophthalmol Vis Sci 2010; 51(11):6018-6029.

9. MembraneBlue [package insert]. D.O.R.C. International b.v., Zuidland, Netherlands, 2009.

10. Veckeneer M, Mohr A, Alharthi E, et al. Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment. Acta Ophthalmol 2014;

92(4):339-344.

11. Mohr A, Bruinsma M, Oellerich S, et al; International Chromovitrectomy Collaboration. Dyes for eyes: hydrodynamics, biocompatibility and efficacy of 'heavy' (dual) dyes for chromovitrectomy. Ophthalmologica 2013; 230(suppl 2):51-58.

12. Jackson TL, Marshall J. Fluorophore-assisted retinal break detection using antibodies to glial fibrillary acidic protein. Invest Ophthalmol Vis Sci 2004; 45(3):993-1001.

13. Menezo JL, Suarez R, Francés J. Clinical survey of the forms, number and localization of retinal tears in cases of relapses and recurrences in retinal detachment. Ophthalmologica 1977; 174(4):210-216.

14. Ashrafzadeh MT, Schepens CL, Elzeneiny II, Moura R, Morse P, Kraushar MF. Aphakic and phakic retinal detachment, I: preoperative findings. Arch Ophthalmol 1973; 89(6):476-483.

15. Cousins S, Boniuk I, Okun E, et al. Pseudophakic retinal detachments in the presence of various IOL types. Ophthalmology 1986; 93(9):1198-1208.

16. Wong D, Billington BM, Chignell AH. Pars plana vitrectomy for retinal detachment with unseen retinal holes. Graefes Arch Clin Exp Ophthalmol 1987; 225(4):269-271.

17. Desai UR, Strassman IB. Combined pars plana vitrectomy and scleral buckling for pseudophakic and aphakic retinal detachments in which a break is not seen preoperatively. Ophthalmic Surg Lasers 1997; 28(9):718-722.

18. Brazitikos PD, D'Amico DJ, Tsinopoulos IT, Stangos NT. Primary vitrectomy with perfluoro-N-octane use in the treatment of pseudophakic retinal detachment with undetected retinal breaks. Retina 1999; 19(2):103-109.

19. Kocaoglan H, Ünlü N, Acar M, Sargin M, Aslan BS, Duman S. Management of rhegmatogenous retinal detachment without detectable breaks. Clin Experiment Ophthalmol 2002; 30(6):415-418.

20. Tewari HK, Kedar S, Kumar A, Garg SP, Verma LK. Comparison of scleral buckling with combined scleral buckling and pars plana vitrectomy in the management of rhegmatogenous retinal detachment with unseen retinal breaks. Clin Experiment Ophthalmol 2003; 31(5):403-407.

21. Salicone A, Smiddy W, Venkatraman A, Feuer W. Management of retinal detachment when no break is found. Ophthalmology 2006; 113(3):398-403.

22. Jackson TL, Kwan AS, Laidlaw AH, Aylward W. Identification of retinal breaks using subretinal trypan blue injection. Ophthalmology 2007; 114(3):587-590. Epub 2006 Nov 21.

23. Rosen PH, Wond HC, McLeod D. Indentation microsurgery: internal searching for retinal breaks. Eye 1989; 3:277-281.

24. Wong R, Gupta B, Aylward GW, Laidlaw DA. Dye extrusion technique (DE-TECH): occult retinal break detection with subretinal dye extrusion during vitrectomy for retinal detachment repair. Retina 2009; 29(4):492-496.

25. Gupta D, Ong J, Burton RL. Trans-scleral dye injection during vitreous surgery to identify clinically undetectable retinal breaks causing retinal detachment. Eye 2011; 25(8):1045-1049. doi: 10.1038/eye.2011.117. Epub 2011 Jun 3.

26. Kim JH, Bertram KM, Quirk MT, Arroyo JG. Modified external needle drainage of subretinal fluid in primary rhegmatogenous retinal detachment: a prospective, consecutive, interventional, single-surgeon study. Retina 2007; 27 (9):1231-1237.

27. Wu WC, Chen MT, Hsu SY, Chang CW. Management of pseudophakic retinal detachment with undetectable retinal breaks. Ophthalmic Surg Lasers 2002; 33(4):314-318.

28. Martínez-Castillo V, Boixadera A, García-Arumí J. Pars plana vitrectomy alone with diffuse illumination and vitreous dissection to manage primary retinal detachment with unseen breaks. Arch Ophthalmol 2009; 127(10):1297-1304. doi: 10.1001/archophthalmol.2009.254.