Epiretinal membranes and neural plasticity of the retina
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Testing for HTB: Trypan blue injected into BSS 1) mixed with PBS, 2) glucose 5%, 3) glucose 5% & methylcellulose, 4) methylcellulose
Chapter 2

Heavy trypan blue staining of epiretinal membranes: an alternative to infracyanine green

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Abstract

Purpose: By using dyes, it is easier to identify the extent of an epiretinal membrane (ERM) or the inner limiting membrane (ILM) during surgery. Trypan blue stains ERM and ILM weakly, but with less apparent toxicity than other intraocular dyes. Its main drawback in vitreoretinal surgery is the requirement of an air-fluid exchange (AFX) prior to its use. We propose a modified form of trypan blue denser than water, thus obviating the need for an AFX. This abstract refers to a prospective, consecutive trial with heavy MembraneBlue® in vitreoretinal surgery.

Methods: A consecutive group of patients with epiretinal membranes was recruited prospectively. Patients were operated using conventional methods. Heavy trypan blue was prepared by mixing glucose 10% with MembraneBlue® (Dorc, Zuidland, The Netherlands) isovolumetrically. Patients were preoperatively and postoperatively assessed at 3 and 6 months (vision and OCT). Ease of surgery was also assessed.

Results: Twenty nine eyes were included in the study. Reapplication of dye was necessary in 25% of the cases, leading to improved contrast further facilitating the peeling process. In no case was an AFX necessary to obtain sufficient staining. All ERM patients had an improvement in vision (from median 0.30 to 0.55) and macular volume and foveal thickness (from median 450 mm to 238 mm) on OCT. No retinal detachment or other complications developed as a result of surgery.

Conclusion: Heavy trypan blue can be delivered efficiently to the retinal surface without the need for an AFX. Staining was sufficient to allow a safe and efficient peeling of ERM. Repeat applications were easily performed. Its use was associated with vision improvement and decrease in foveal thickness, and the absence of adverse events in this small case series.
Introduction

Removal of the internal limiting membranes and of idiopathic epiretinal membranes (ERM) requires skill and experience. Non closure of macular holes and reproliferation of macular puckers have both been related to inadequate removal of membranes. To improve the surgical outcome, and to facilitate the conduct of surgery means of enhancing membrane visibility have been sought. These have included indirect means such as the use of a slit beam illumination, triamcinolone, and stains such as ICG, and trypan blue. Due to a superior safety profile as compared to ICG, MembraneBlue® has been used by a number of European surgeons despite its less obvious staining characteristics.

The commercially available version of trypan blue (MembraneBlue®, DORC, Zuidland, The Netherlands) used in vitreoretinal surgery is diluted in phosphate buffered saline, and requires a fluid-air exchange before injecting the dye as it otherwise diffuses though the vitreous cavity and does not stain membranes sufficiently. To avoid the need for a fluid-air exchange we have modified the diluents used with trypan blue to render it denser than saline, BSS+ and other vitreo-retinal infusates. This solution requires the addition of a fixed volume of concentrated glucose solution to achieve the necessary density.

Using this modified “heavy” trypan blue solution, we conducted a prospective, consecutive study of 30 patients with idiopathic epiretinal membranes, to assess the staining characteristics, ease of use, and safety of the heavy trypan blue in vitreoretinal surgery.

Methods

Patients with either idiopathic ERM or secondary ERM due to retinal detachment surgery or trauma were recruited prospectively and consecutively into this study. Appropriate approval from the hospital medical ethics committee was obtained as dictated by Dutch law for this type of medical investigation. Appropriate consent was obtained. Preoperative assessment included age, gender, best corrected visual acuity (BCVA) and full ocular examination. Ocular coherence tomography (OCT) was performed using the OCT3 (Zeiss, Inc Jena, Germany) to measure macular thickness and volume changes caused by the ERM (fast macular thickness protocol). Postoperatively best corrected visual acuity and OCT were repeated at 3 months.

Patients were operated using conventional methods using a 3 port, 20 gauge vitrectomy. After full vitrectomy the infusion line was turned off and heavy MembraneBlue® was injected over the macular area and left for 2 minutes (figure 1). Heavy trypan blue was prepared by mixing equal volumes of glucose 10% with commercially available trypan blue 0.15%
(MembraneBlue®, DORC, Zuidland, NL). This provides a final glucose concentration of 5% and a final trypan blue concentration of 0.075%. The osmolality of this solution is 320 mosm and pH neutral. Following the 2 minute incubation, the infusion was once again opened and the excess dye was removed using a silicone tipped Charles flute (figure 2). Membrane peeling was achieved using a combination of a pic needle or bent MVR blade and Eckhardt microforceps (DORC, Zuidland, The Netherlands) (figure 2). The staining procedure was repeated in some patients where staining was initially inadequate, or to find a membrane edge, or in whom a doubt persisted regarding the complete removal of the membrane. After the membrane was fully removed, an internal search was performed and the sclerostomies and conjunctiva were closed.

**Results**

A total of 29 eyes in 29 patients were recruited in this study. Mean age was 67 years (range 37-83). 13 Patients were female, 18 male. 16 patients were phakic, 15 pseudophakic. 14 of the ERM s were idiopathic, 3 with a lamellar hole, 3 were post trabeculectomy, 6 post retinal detachment, and 1 post endophthalmitis, 1 post trauma, 1 high myope with a staphyloma and 2 diabetics. Preoperative BCVA ranged from 0.01 to 0.63 (mean 0.31, median 0.32). On OCT the preoperative foveal thickness ranged between 309-680 (mean 435, median 439)
and the macular volume range was 7.3 to 13.5 (mean 9.5, median 9.1). Post operative BCVA varied from 0.12-1.0 (mean 0.55, median 0.50). Post operative foveal thickness improved to a mean of 238 (median 330) and macular volume improved to a mean value of 7.49 (range 8.03).

BCVA was improved or maintained in all patients. In 2 patients vision did not improve, but they noted an improvement in metamorphopsia. Nineteen (64%) patients improved two or more lines of vision. All patients were followed up for a minimum of 3 months. During follow-up, none of the patients had a retinal detachment, macular pigment alteration, or other complications.

**DISCUSSION**

Removal of epiretinal membranes can be a challenge in vitreoretinal surgery. Using dyes to stain epiretinal membranes can facilitate a more complete removal. The staining method must be safe easy to apply and use.

Indocyanine green has been used for both epiretinal membrane and macular hole surgery. It gives an intense stain of both ERM and ILM. However there have been reports of adverse
effects on outcome and toxicity for the retinal pigment epithelium\textsuperscript{5,6}. This toxicity could affect visual recovery after surgery\textsuperscript{7}.

Trypan blue was initially used to stain the lens capsule (0.06\% trypan blue in Vision blue)\textsuperscript{8} and then to stain preretinal structures in 0.15\% concentration in MembraneBlue\textsuperscript{®} (DORC). Feron \textit{et al.} initially described the use of TB for removing membranes in proliferative vitreoretinopathy\textsuperscript{9}. After which it was described for epiretinal membrane peeling and ILM peeling in concentrations varying from 0.06\% to 0.2\%. These concentrations were not found to be toxic to rabbit retina if removed promptly\textsuperscript{10} and non toxic to cultured retinal pigment epithelial cells in concentrations of 0.06\% to 0.3\% for 5 minutes. None of these concentrations were reported as toxic in clinical practice. Haritoglou \textit{et al.} found visions after ERM removal at 6 months to be similar between eyes operated with and without trypan blue. This suggests that trypan blue does not have a negative influence on visual outcome\textsuperscript{11,12}. Balayre \textit{et al.} performed multifocal ERG on patients operated for epiretinal membrane using 0.15\% trypan blue and found no decrease in macular responses and an increase 4 months after surgery\textsuperscript{13}.

The main disadvantage of MembraneBlue\textsuperscript{®}, as formulated in MembraneBlue\textsuperscript{®} is that an air-fluid exchange is necessary to achieve adequate staining. AFX in itself increases risk for surgical complications including retinal tears. To eliminate the need for an AFX, we proposed a heavy form of TB which can be applied into a fluid filled eye without dispersing. Staining characteristics using this approach are sufficient to allow an efficient peeling of the membrane following an appropriate flush of the left over dye. The mixture of trypan blue with 10\% glucose facilitates its use during surgery. By eliminating the need for a fluid air exchange, repeat application of the dye can also be easily and rapidly carried out. This leads to a more complete removal of the membrane without having a negative effect on vision. All patients in our study had an improvement of retinal thickness on ocular coherence tomography and no patients had a decrease in vision.

We would like to conclude that trypan blue rendered “heavy” by mixing it isovolumetrically with glucose 10\% is a safe way of staining epiretinal membranes, whilst also eliminating the need for an air-fluid exchange. None of our patients lost vision and 64\% improved more than 2 lines at 3 months. All patients had a decrease in macular thickness and volume.
REFERENCES


