The efficacy of vital dyes in PVR surgery

A variety of dyes stain different ocular structures.

Transparent tissues such as the posterior hyaloid, the epiretinal membrane (ERM) and the internal limiting membrane (ILM) play an important role in multiple diseases. Staining of these tissues with vital dyes may facilitate their identification and safe removal during vitreoretinal surgery. Several dyes are currently in routine clinical use for chromovitrectomy to visualise different structures in the eye.

Vitreoretinal surgery is performed for a variety of retinal diseases, including symptomatic vitreomacular adhesion, diabetic macular oedema, macular hole, and epiretinal membrane (ERM). Vitreous traction from the posterior hyaloid on the retinal surface has been linked to the pathogenesis of proliferative vitreoretinopathy (PVR), proliferative diabetic vitreoretinopathy (PDVR) and other conditions. Surgery attempts to release the three predominant tractional components from the retinal surface including the posterior hyaloid, the ERM, and the internal limiting membrane (ILM).

The main difficulty remains to visualise the thin and semitransparent structure, namely the vitreous or the internal limiting membrane (ILM). Different various intraocular structures have a different affinity to different dyes: while triamcinolone acetonide (TA) may be used to stain the vitreous and posterior hyaloid, trypan blue (TB) stains cellular structures e.g. the ERM, indocyanine green (ICG) has a good staining affinity for the ILM. In 2008, we summarised for the first time the benefits and potential risks of vital dyes in chromovitrectomy in a textbook (Meyer, 2008) and formed an 'International Chromovitrectomy Initiative'. For the EURETINA meeting 2013 we summarised the key developments and novel perspectives in a separate supplement issue in the Journal Ophthalmologica.

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Vitreous staining

A better and complete separation of the posterior hyaloid is the main goal in any vitrectomy. Fluorescein, triamcinolone acetonide (TA), ICG, and trypan blue (TB) may be used to highlight the fibers of the vitreous. TA was found to provide the best visualisation of the vitreous. Upon TA injection into the vitreous, the agent facilitates the identification of remaining vitreous. In addition, TA is a well-tolerated corticosteroid, widely used in ophthalmology. Thus, remaining TA particles may also reduce breakdown of the blood-aqueous barrier and preretinal fibrosis. TA is currently most widely used to visualise the posterior hyaloid. After removal of the vitreous from the retinal surface the peeling of epiretinal membranes and PVR becomes apparent.

Epiretinal membrane

The removal or peeling of the epiretinal membranes is an essential procedure in PVR surgery to release traction and unfold contracted retinal tissue. The structure of these membranes can range from opaque or dense to fine and semitransparent tissue. The affinity and firmness of these attachments may vary from case to case and can be challenging, even for experienced surgeons.

TB provides good staining of the ERM, but poor ILM staining at a concentration of 0.15 %, a relatively safe dose in clinical trials. Experimental studies, however, indicate that concentrations greater than 0.3 % may be toxic. TB remains the most frequently used choice for the peeling of ERM or PVR to date.

Internal limiting membrane

The ILM may serve as a scaffold for cellular proliferation leading to traction and the formation of ERM or PVR. Its removal helps to ensure that ERM and PVR tissues have been completely removed and also reduces the risk of recurrence. ICG and BBG bind well to the acellular structure of the collagen fibres of the ILM. Both dyes provide good contrast of the ILM and surrounding tissues; the binding also increases the stiffness of the ILM, making peeling of the membrane easier.

Although ICG has initially been used on a routine basis, the dye has been reported to cause RPE atrophy during macular hole surgery, due to the osmolarity of the ICG solution, decomposition of the ICG molecule, the effect of iodine, carbolinic complex formation and the oxidative effect due to singlet oxygen release from the ICG molecule after light exposure. A meta-analysis of ILM peeling in MH surgery with and without ICG showed similar anatomic closure rates with both approaches, but statistically worse functional outcomes when ICG was used (P = 0.0008).

Brilliant blue (BBG) has been used as an alternative dye, as it has also a high affinity for the ILM and does not stain the ERM. The different affinity of BBG to both tissue layers is advantageous as the unstained ERM (negative staining) is clearly depicted against the bluish stained ILM. After removal of the ERM, the accurate visualisation of the ILM remains difficult. BBG showed no signs of toxicity in animal experiments and appears to be safe in concentrations of up to 0.25 mg/ml. In addition, BBG was recently characterised as an antagonist of the purinergic receptor P2RX7, which is implicated in the pathway of pathologic loss of photoreceptors. All hallmarks of photoreceptor apoptosis were prevented by premedication or co-application of BBG. The study suggested that BBG has a potential application as a neuroprotective agent in retinal diseases or similar neurodegenerative pathologies linked to excess extracellular ATP.

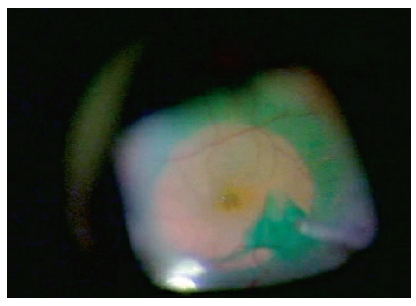

Fig. 1: ILM-staining with indocyan green in macular hole surgery

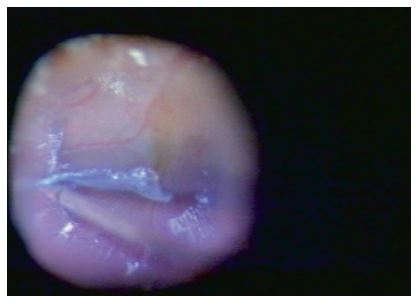

Fig. 2: Staining the epiretinal membranes (ERM) with trypan blue after TA-guided vitreous removal.

Other Dyes

The ideal dye for ocular tissues would provide excellent contrast, high biocompatibility combined with no toxicity to achieve the best functional and anatomical outcome for the patient. It should be absorbed at visible wavelengths, bind selectively to tissues of interest, and be physiologically degradable on a practical time scale. The safety profile of numerous dyes including light green, fast green, infracyanine green, indigo carmine, evans blue and bromophenol blue has been evaluated. Rodrigues et al. reported on the abilities of 13 dyes to stain the lens capsule, ERM, ILM, and vitreous. BBG demonstrated the best ILM staining of all dyes under evaluation. Haritoglou and colleagues described the staining and biocompatibility properties of a new cyanine dye 3,3'-Di-(4-sulfobutyl)- 1,1,1',1'-tetramethyl-di-1H-benz[e]indocarbocyanine (DSS) for ILM peeling and found excellent ILM staining. Sousa-Martins and colleagues evaluated the use of a natural dye solution of lutein and zeaxanthin alone and in combination with BBG. In 60 post-mortem eyes, they found a precipitate of lutein and zeaxanthin on the vitreous surface, staining it orange. A precipitate of lutein and zeaxanthin (20%) crystals combined with BBG showed high affinity for the ILM and has potential in intraocular surgery.

Lately, Chen and colleagues evaluated 11 anthocyanin dyes from acai fruit (Euterpe oleracea), pomegranate (Punica granatum), logwood (Haematoxylum campechianum), chlorophyll extract from alfalfa (Medicago sativa), cochineal (Dactylopius coccus), hibiscus (Hibiscus rosa-sinensis), indigo (Indigofera tinctoria), paprika (Capsicum annuum), turmeric (Curcuma longa), old fustic (Maclura tinctoria), and grape (Vitis vinifera). Using these dyes for ILM peeling in post-mortem eyes was similar to ILM peeling with ICG in our hands. Although all the dyes facilitated PVD and ILM peeling in cadaveric eyes, best ILM staining was obtained with acai fruit extract, cochineal, and chlorophyll extract from alfalfa. ■

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Main Session 9:
PVR & Retinal Detachment
Room: Hall 1
Date: 29-09-2013
From: 8:00 to: 10:00

Tracking the progression of diabetic retinopathy

The RET02 Trial is designed to study phenotypes of retinopathy progression in type 2 diabetes.

Nonproliferative diabetic retinopathy (NPDR) is the earliest stage of diabetic retinopathy, characterised by damaged blood vessels in the retina that begin to leak into the eye. In the RET02 trial, the turnover of microaneuryms and retinal thickness at baseline showed a wide range of values, indicating that different vascular and neuronal components of the disease process may be involved in disease progression.

The RET02 trial is a one-year observational and prospective study to identify phenotypes of retinopathy progression. 375 type 2 diabetic patients (65.4% males and 34.6% females at the age of 35 to 82 years) with mild NPDR (ETDRS levels 20 or 35) were enrolled. The trial was conducted at 19 clinical sites of the European Vision Institute Clinical Research Network (EVICR.net); it started in September 2010 and was concluded in July 2013.

José Cunha-Vaz

Four visits were scheduled at months 0, 3, 6 and 12 with the following examinations: colour fundus photography (CFP), spectral domain optical coherence tomography (SD-OCT) and blood tests. ETDRS severity levels at the first and last visits and microaneurysm (MA) turnover (formation plus disappearance rates), as assessed by the RetmarkerDR®, were evaluated by the Coimbra Ophthalmology Reading Centre (CORC).

SD-OCT Cirrus and/or Spectralis were used to measure retinal thickness (RT), nerve fibre and ganglion cell layers. One eye per patient was selected by the Reading Centre as the study eye. At baseline, the mean best-corrected visual acuity (BCVA) was 84.8±6.6 ETDRS letters. Mean HbA_{1C} was 7.8±4.2%; the numbers of systolic and diastolic blood pressure were 137.7±16.6 and 77.4±10.1 mmHg, respectively. Eyes/patients showed a mean number of MA of 3.6±5.2 at baseline. The mean retinal thickness in the central subfield was 265.0±21.8 µm for Cirrus OCT and 278.4±26.6 µm for Spectralis OCT. Males showed a higher retinal thickness than females ($p<0.05$). A wide range of abnormal RT values was observed, from higher to lower values. Comparing the mean RT in the central subfield with normal RT values (mean±2SD), 8.6% of the eyes/patients showed a decreased RT, and 8.3% of the eyes/patients showed an increased RT. ■

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EVICR.net Session
Room: Hall F
Date: 28-09-2013
From: 14:30 to: 16:00