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Which colour suits the vitreoretinal surgeon?

Which colour suits the vitreoretinal surgeon?

Nanny Collaer, Peter Stalmans

Finding the true colour

Vitreoretinal surgery underwent major innovative changes over the past few years in the treatment of traction maculopathies, such as macular puckers and macular holes. The complete removal of epiretinal tissue from the posterior pole is a prerequisite for maximal functional recovery after surgery.^{1–4} However, the peeling of an optically semitransparent layer of tissue, which is only a few micrometers thick, such as epiretinal membrane (ERM) and internal limiting membrane (ILM), remains a surgical challenging manoeuvre, even for the more experienced vitreoretinal surgeons. In view of this, the introduction of vital stains allowed precise preoperative identification and delineation of ERM and ILM, enabling surgeons to perform peeling procedures with improved safety and ease. The concept of chromovitrectomy was born and staining tissues during vitreoretinal surgery became a popular procedure.

Since a number of years, three dyes are commonly used in current ophthalmic surgery: indocyanine green (ICG) and infracyanine green, exhibiting an affinity for the acellular ILM;⁵ and trypan blue, merely staining cellular structures such as epiretinal membranes but also, to a lesser degree, the ILM.^{6–8} ICG was the first dye to be introduced as a macular stain.⁸ Known for its use in choroidal angiography, it has become widely adopted for enhanced visualisation of ILM during macular hole surgery.^{5, 8–11} However, there is growing evidence of ICG-related toxicity when applied intraocularly, causing retinal damage by phototoxicity¹² and the osmolarity¹³ of ICG. Both in vitro^{12–17} and

in vivo experiments^{18, 19} have shown possible toxic effects. The initial enthusiasm was replaced by a bittersweet taste and the issue on ICG toxicity remains the subject of heavy debate (Annual Meeting of the American Academy of Ophthalmology, 2006).

Owing to the potential retinal pigment epithelial toxicity associated with the use of hypo-osmotic ICG solution, infracyanine green was advocated as an alternative vital stain^{20, 21}—less likely to induce osmolarity related toxic effects on the retinal pigment epithelial cells because of its iso-osmotic solvent.¹³ ICG contains iodine to enhance its solubility in pure water. Infracyanine green does not contain iodine, precipitates in water and must be dissolved in glucose 5%. However, experimental studies suggested possible toxic effects for the use of infracyanine green too.^{16, 22, 23}

Consequently, trypan blue arose as the second generation of ophthalmic dyes. Trypan blue was first used to facilitate anterior segment surgery in staining the anterior lens capsule to facilitate circular curvilinear capsulorhexis in patients with mature cataracts,²⁴ and in evaluating the corneal endothelium of donor tissue prior to penetrating keratoplasty through identification of devitalised endothelial cells.²⁵ Its safety was demonstrated in rabbit studies²⁶ and because of its affinity to ERM, and to a lesser extent to ILM, it soon became a commonly used dye, making it useful for both macular hole and macular pucker surgery.^{6, 7, 21, 27–32} However, there are conflicting reports about the safety of trypan blue. No adverse clinical events have been

reported, but there is an ongoing debate about the toxicity in cell culture models with several authors reporting on toxicity^{23, 33–36} and others reporting on safety.^{16, 37–42}

It appears that the above-mentioned vital stains were introduced as dyes in chromovitrectomy because clinicians were familiar with the use of this readily available dye in other fields. ICG had a history as a diagnostic tool for choroidal angiography and trypan blue had proven to be useful in anterior segment surgery. Under those particular applications, ICG and trypan blue had not shown any adverse effects; however, extensive experimental studies on the safety for their particular use as macular stains had not been undertaken prior to their introduction as an intraocular dye for vitreoretinal procedures.

Because of the limitations of ICG and trypan blue, with possible toxic effects that cannot be excluded, alternative dyes are anticipated. Novel vital stains with a broad safety margin and superior membrane staining potential are being investigated. A systematic step-by-step approach to evaluate new potential intraocular dyes has been proposed, with preliminary ex vivo safety testing prior to animal and then human studies.^{43, 44}

Here we want to refer to the work in this issue of *BJO* by Haritoglou *et al* (see page 1125).⁴⁵

In earlier work they demonstrated in an ex vivo experimental setting the biocompatibility of certain dyes in different cell culture models, one of the dyes being bromophenol blue that showed no relevant toxicity in vitro.⁴³ Two in vivo experiments became the next step in their systematic approach. Bromophenol blue revealed satisfactory staining characteristics during short-term investigations in porcine eyes⁴⁶ and did not produce a histologically detectable toxic effect on the retina in an in vivo rat model.⁴⁷ In view of these findings, both ex vivo and in vivo, which demonstrated excellent staining characteristics and biocompatibility for bromophenol blue, Haritoglou *et al* now present the first series of patients in whom the application of bromophenol blue as a macular stain was used in the

treatment of macular puckers and macular holes.

We can only encourage this systematic approach in an attempt to find the ultimate dye, which allows the vitreoretinal surgeon to adequately remove epiretinal structures and internal limiting membrane, without the risk of exposing the patient to possible toxic side-effects, and therefore eliminating any benefit over a non-dye assisted vitreoretinal procedure. There is no doubt that enhanced visualisation of diaphanous structures through the use of vital stains during vitreoretinal surgery will facilitate the procedure, but this can only be justified if no iatrogenic risks are associated with its use. This approach will hopefully result in finding the true colour that perfectly suits the vitreoretinal surgeon.

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