Indocyanine green accused

T L Jackson

The case for and against ICG assisted macular surgery

The concept of retinal vital staining is not new. There has however been renewed interest in the subject since indocyanine green (ICG) was introduced as a vital stain to highlight the internal limiting membrane (ILM) during macular surgery. ICG’s well known role in cardiac and choroidal angiography exploits its properties as a fluorophore, but its role as a macular vital stain relies on its properties as a chromophore or biological stain. Biological stains such as ICG have specific atomic groupings that impart a chromophore or biological stain. Fluorophore, but its role as a macular surgery. ICG’s well known internal limiting membrane (ILM) duration as a vital stain to highlight the indocyanine green (ICG) was introduced several weeks. In addition, the use of ICG, with exposure times of 30 seconds or less. In addition, many investigators dissolved ICG in 0.5 ml of distilled water, before mixing with 4.5 ml of a balanced saline solution (BSS). This produces a 275 mOsm solution that is hypo-osmotic relative to agents such as BSS (302 mOsm). It has been suggested that ICG toxicity is caused, or at least aggravated, by low osmolarity.

The experimental reports of ICG toxicity are also imperfect. One of the most influential studies exposed human cadaveric eyes to ICG and illumination with a surgical endolight. The selected histological images were dramatic, with profound disruption of cellular architecture. This is not consistent with clinical observations, as reports of ICG toxicity generally show only mild to moderate deficits. Other authors were not able to repeat these observations in freshly enucleated pig eyes. Further, the validity of using enucleated eyes to model vascularised, viable retina is uncertain. And the verdict? A good judge will want to hear more evidence.

Studies of surgical ILM specimens have included retinal cellular elements and this has been marshalled as evidence that ICG alters the cleavage plane during ILM removal. However, this has also been observed in studies that did not use ICG. Cell culture experiments also need to be interpreted cautiously, as they do not simulate the complex interactions of a multicellular environment such as the retina. Many authors relied on a mitochondrial dehydrogenase enzyme assay to measure cell viability, yet there is spectral overlap of ICG absorption and the blue formazan reaction product that this assay reads. Without careful rinsing routines or appropriate assay correction, it is possible that residual ICG may produce falsely low readings of viability in a concentration dependent manner. This may explain why some papers showed more damage with this technique than with ultrastructural analysis. Potentially useful live animal studies showing histological or electrophysiological damage failed to model the clinical use of ICG, with exposure times of several days.

It should be noted that not all experimental studies show that ICG is unsafe. Retinal pigment epithelium (RPE) and glial cell culture studies, as well as macular surgery in enucleated pig eyes, all found that at least some clinically useful preparations did not cause damage.

As in the case supporting ICG use, the case against ICG can be considered in terms of the clinical and experimental evidence. Clinical studies have shown visual field defects, loss of VA, and RPE atrophy. The only randomised trial of ICG vital staining showed a small but significant reduction in VA, albeit using a hypo-osmolar preparation. Of particular concern are reports showing the persistence of ICG for several weeks. In addition, the use of ICG may be harder to justify now that 0.15% trypan blue is available as an alternative chromophore (Membrane Blue, Dorc, Netherlands).

There are experimental studies showing ICG toxicity in RPE, Müller cells, retinal ganglion cells, and both ex vivo and in vivo whole retina. The fact that so many investigators found evidence of cell damage cannot be ignored, even if exposure routines were sometimes dissimilar to those used clinically.

Advocates of ICG may suggest that infracyanine green is a safe alternative but this may not be so. Infracyanine green (Serb, Paris, France) is similar to ICG, but does not contain iodine and comes with 5% glucose as the diluent. Some investigations suggest that this alters the absorption profile, reducing the risk of ICG mediated phototoxicity when cells are illuminated. However, experiments in cadaver eyes also show cell damage, and Hillenkamp’s paper suggests that the effect on the absorption profile may be less than initially thought.

And the verdict? A good judge will want to hear more evidence. What is needed experimentally is a well controlled study that includes vitrectomy,
short exposure times, then careful histo-
tological and electrophysiological analy-
sis—preferably in an animal with rods,
cones, and a duplex retinal circulation. 
Although difficult in some species, 
surgery would ideally include posterior 
vitreous detachment and removal of the 
ILM. Clinically, an appropriately sized, 
preferably multicentre, randomised trial 
is needed using an iso-osmotic, low 
centration distance up and power down, 
concentration. Its place in the surgical manage-
ment of ICG in the consent process may be 
neous. Another suggested technique involves 
immediately after dye application. 
short exposure times, then careful his-
logenously avoiding hypo-osmotic 
parameters measured in Hillenkamp’s 
alkaline light sources, and rinsing fully and 
with an iso-osmotic, low 
negative risk of visual loss. The literature 
suggests using a low concentration (0.5–
2.5 mg/ml), avoiding hypo-osmotic 
sources. In Hillenkamp’s 
KL. Clinically, an appropriately sized, 
reset use to difficult 
ism, and appropriate outcome measures. The 
parameters measured in Hillenkamp’s 
alden’s paper represent a useful template, but 
yes. Until such trials are completed, clin-
icians who continue to use ICG have 
some guidance from the literature in 
terms of reducing potential risk. One 
suggestion is to restrict use to difficult 
cases, where the surgical assistance 
offered by ICG is likely to outweigh 
any risk of visual loss. The literature 
suggests using a low concentration (0.5–
1.25 mg/ml), avoiding hypo-osmotic 
preparations, keeping the endo-illumi-
nation distance up and power down, 
selecting halogen rather than xenon 
light sources, and rinsing fully and 
mediation techniques. In 1969 
Molteno launched the concept of a tube 
and plate for glaucoma drainage, in which 
the plate is secured onto the episclera, 
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orificial bleb. Contemporary GDDs, which dominate the market are 
the Molteno, Krupin, Baerveldt, Ahmed, 
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the essential design concept of posterior 
staining of the internal limiting membrane using 
glucose 5% diluted indocyanine green and 
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If glaucoma drainage devices do offer substantial surgical possibilities for refractory glaucoma they also present disadvantages, either overflow of aqueous onto the anterior chamber or poor filtration with IOP elevation.

Contact between the tube and the corneal endothelium may also induce a long term corneal decompensation. To minimise the rate of early postoperative hypotony, some of the devices contain a valve mechanism that restricts the aqueous outflow. However, owing to the relatively high postoperative complication rates and the relatively difficult and traumatic implantation procedure, the use of GDDs is usually limited to complicated cases after other modes of treatment, both surgical and non-surgical, have failed.

Past experience with GDDs reveals that material composition, implant design, physicochemical surface properties, condition of the host bed, surgical technique, and mechanical properties influence the eye’s response to the device. All of these factors may influence the overall performance and surgical outcome.

The Ex-PRESS implant is a miniature unvalved glaucoma implant. It was developed as an alternative procedure to trabeculectomy and to the other types of glaucoma filtering surgery for patients with primary open angle glaucoma (POAG). The device is a 3 mm long stainless steel tube (outer diameter 400 µm (27 gauge)) with a bevelled, sharpened, rounded tip, a disc-like flange and inner spur are angled to conform to the anatomy of the sclera, and the distance between them corresponds to the scleral thickness at the site of implantation.

Originally, the device was designed to be inserted at the limbus directly under the conjunctiva. In this case, a subconjunctival bleb is formed and serves as a flow modulator. This technique is relatively simple and can be performed in a few minutes, either on its own or in combination with phacoemulsification.

The paper by Traverso et al in this issue of the journal summarises a 3 year follow up with the device. Success rate and short term complications, such as a shallow or flat anterior chamber and hypopla are comparable favourably with data reported in the literature for trabeculectomy.

However, some patients encountered poor conjunctival covering of the device. Several conjunctival erosions were noted over the external flange. Conjunctivoplasty or tube removal had to be performed to avoid secondary infection. On the other hand, several patients showed conjunctival scarring with subsequent decreased aqueous humour filtration.

To overcome this complication of conjunctival erosion and bleb fibroses, Dahan and Carmichael recently suggested implanting the device under a limbus based 50% deep scleral flap extending into clear cornea. This operation is similar to standard trabeculectomy without the need of an iridectomy or scleral removal. This may offer an advantage over standard trabeculectomy. Early findings from Sherwood on rabbits (Ex-PRESS filtering shunt bleb TGF-ß levels in rabbit model, personal communication, October 2004) reveal that the “less invasive technique reduces ocular inflammation by decreasing TGF-ß levels in aqueous humour.”

The rationale behind this surgical modification is to increase the resistance to aqueous flow in the early postoperative stages as well as to reduce the development of late conjunctival erosion. This technique therefore potentially reduces the complications of hypotony, especially in patients at high risk of surgical failure. Furthermore, the 2 year postoperative reduction in IOP in the study of Dahan et al was >40% and only 10% of the patients required further medical therapy.

This tube may also be used in deep sclerectomy to simplify the difficult dissection of Schlemm’s canal and trabeculo-Descelet’s membrane. In an unpublished study, we found that by performing a partial posterior deep sclerectomy and inserting an Ex-PRESS implant into the anterior portion under the superficial scleral flap, we obtained excellent IOP reduction with very few postoperative complications. This technique drastically simplifies the surgical dissection of deep sclerectomy and yet still provides its outflow advantage including the drainage of the aqueous to (1) a subconjunctival bleb, (2) an intra-scleral bleb, and (3) the subchoroidal space.

Used in deep sclerectomy, the Ex-PRESS tube also avoids the late need for gonipuncture (Mermoud et al, unpublished data).

Initial doubt about the Ex-PRESS implant are decreasing with recent advances offering possibly a wider spectrum of indications while diminishing the potential complications.

The Ex-PRESS implant was introduced to offer a quick and simple alternative to glaucoma surgery. The procedure is indeed rapid; however, it may be associated with new complications such as conjunctival erosion and risk of subsequent infection. The modification in the technique by introducing the tube under a superficial scleral flap seems to overcome these complications.

Further research and clinical studies will allow us to discover whether the Ex-PRESS tube will definitely change our approach to glaucoma surgery.

REFERENCES


CATARACT SURGERY

Is one trial enough?

R Wormald

Is this sufficient evidence to change practice?

In the March issue of BJO a randomised controlled trial was reported in which topical versus sub-Tenon's local anaesthesia for routine cataract surgery is compared. The trial is well designed and simple, using a validated outcome measure with the outcome observers masked to the intervention. It shows a clear preference for sub-Tenon's block by patients undergoing routine cataract surgery. The trial is well conducted randomised trials add to the body of evidence. It may be difficult to decide there is sufficient evidence to conduct the definitive experiment. The trialists may need to reappraise the study design and the size of effect that is clinically relevant, then perhaps apply more stringent criteria for the control of an alpha error. It will be the duty of the research ethics committees to make a decision about continuing to withhold the treatment found to be advantageous in the pilot study.

This study, despite being small, is of value and it is right that it should be published, since all results from properly conducted randomised trials add to the body of evidence (even if only in a small way) and should be available in the public domain for all to see. This may soon become a statutory requirement in the United States if legislation to prospectively register all randomised controlled trials, and make their results available to all, becomes law.

This will be a major step forward for evidence based medicine since it will lock the pharmaceutical industry, as well as everybody else, into making the results of all their trials, whether positive or negative in outcome, publicly available.

The body of evidence grows as experiments are repeated. Another properly powered trial with a sample size calculation and with similar findings has been published in the British Journal of Anaesthesia since Rüschten et al's paper was accepted. These studies should now be summarised in a properly conducted systematic review. One such review has been published and would appear to support the findings of this study.

Another Cochrane review is under way which will include the findings of this trial and the other recently published one. Surgeons wanting to make decisions about changing their practice may decide there is sufficient evidence to do so but others may wish to await a larger body of evidence. It may be difficult to justify another trial comparing sub-Tenon's with topical anaesthesia alone but some will argue that intracameral lignocaine would make a major difference to the comparison. Thus, further trials are needed to address this question.


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REFERENCES