Capsule Staining as an Adjunct to Cataract Surgery

A Report from the American Academy of Ophthalmology

Deborah S. Jacobs, MD, Terry A. Cox, MD, PhD, Michael D. Wagoner, MD, Reginald G. Ariyasu, MD, PhD, Carol L. Karp, MD

Objective: This document evaluates currently available data in the published literature to answer the question of whether the use of dye such as indocyanine green or trypan blue to stain the lens capsule to improve visualization is safe and effective as an adjunct to cataract surgery.

Methods: Literature searches conducted in March 2003 and May 2004 retrieved 139 citations. The panel members reviewed the abstracts and selected 47 of possible clinical relevance for review. An additional 14 articles were identified for evaluation. Of the 61 articles reviewed, the panel members selected 36 for the panel methodologist to review and rate according to the strength of the evidence. A level I rating was assigned to properly conducted, well-designed, randomized clinical trials; a level II rating was assigned to well-designed cohort and case–control studies; and a level III rating was assigned to case series and case reports.

Results: There is level III evidence that indocyanine green, trypan blue, and fluorescein are each effective in staining the lens capsule and that indocyanine green and trypan blue provide better ease of use and visualization of the capsule than fluoroscein. There is level II evidence that staining the capsule is helpful in completing capsulorrhexis and that it is helpful for pediatric patients under age 5 years and in cases of white cataract. The overall surgical advantage of a completed continuous curvilinear capsulorrhexis using dye has not been demonstrated, but this may be related to the outcome measures chosen rather than a failure to confer advantage. There are substantial data indicating that trypan blue 0.1% is not toxic to the cornea. There are limited data suggesting that indocyanine green 0.125% to 0.5% is not toxic to anterior segment structures.

Conclusions: There are data confirming that dye is safe and effective as an adjunct for capsule visualization in cataract surgery. It is reasonable to use dye when inadequate capsule visualization may compromise the outcome in cataract surgery. More studies are needed to confirm a lack of toxicity of indocyanine green and trypan blue, particularly in the event of posterior segment or longer duration exposure. *Ophthalmology 2006;113: 707–713 © 2006 by the American Academy of Ophthalmology.*

Introduction

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to evaluate the peer-reviewed published scientific literature to help refine the important questions to be answered by future investigations and define what is well established. After appropriate review by all contributors, including legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements.

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Background

The creation of a continuous curvilinear capsulorrhexis (CCC) in the anterior lens capsule is a critical step in cataract surgery that is performed by phacoemulsification. Anterior and posterior CCCs are also important in pediatric cataract cases in which intraocular lens (IOL) implantation is planned. Visualization of the capsule flap is important to maintain control of the tear as it is being made to ensure that it is continuous. It is crucial that the capsulorrhexis be continuous in cases of advanced cataract that might require higher phacoemulsification energies, more manipulation in the capsular bag, and vigorous cracking and/or chopping in the capsular bag. A tear that has noncontinuous components is likely to develop radial extensions when stressed.[1] These extensions may preclude safe completion of phacoemulsification and implantation of a posterior chamber lOL. Inadvertent placement of one haptic out of the bag[2] and IOL

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decentration and tilt[3] are also more likely in the presence of noncontinuous components in the capsulotomy.

Adequate visualization of the capsule flap to ensure a continuous tear can be compromised under many circumstances. Visualization can be difficult with mature cataracts, which by definition lack a red reflex; traumatic cataracts; cataracts with a white or opalescent cortex; and cataracts in eyes with corneal opacities. Improving capsule visualization may also be of value to those who are learning the techniques of capsulorrhexis and phacoemulsification. Improved visualization of the capsule may be an advantage in pediatric cataract extraction in which IOL implantation is contemplated, because the pediatric capsule can be particularly thin and elastic, making the completion of a continuous capsulorrhexis a particular challenge.

In 1993, a letter reported the use of fluorescein in a mature cataract for improved visualization during capsulorrhexis. In this report, fluorescein was instilled under the anterior capsule in a chamber filled with viscoelastic.[4] Since that time, the use of other dyes and alternative techniques to stain the capsule for improved visualization during cataract surgery have been reported. The dyes that have received the most attention are indocyanine green, trypan blue, fluorescein, crystal violet, and gentian violet.

The usual procedure for staining the capsule during cataract surgery is to instill dye in the anterior chamber (AC) after the initial paracentesis is made. Most frequently, 1 or 2 drops of the dye are instilled into the AC directly onto the anterior capsule surface after the AC is filled with air.[5–8] The air bubble limits contact of the dye to the iris and anterior capsule. Alternatively, dye can be mixed with viscoelastic, instilled under viscoelastic, or instilled into a balanced salt solution under viscoelastic.[9–11] Special cannulae have been devised to facilitate the introduction of dye.[8] Alternatively, dye can be instilled under the capsule after the AC has been filled with viscoelastic. This technique is described for fluorescein, which stains AC structures and is best confined to the posterior surface of the capsule.[4,12] Viscoelastic is then used to drive air and dye out of the chamber. The main wound is constructed as usual, followed by capsulorrhexis and phacoemulsification as usual.

Food and Drug Administration Status

Of the 5 dyes reported in the literature reviewed (indocyanine green, trypan blue, fluorescein, crystal violet, and gentian violet), the Food and Drug Administration (FDA) has approved only indocyanine green, fluorescein, and trypan blue for in vivo use. Only trypan blue is approved for use as an adjunct to cataract surgery. Indocyanine green is approved for IV administration for the purpose of determining cardiac output, hepatic function, and liver blood flow, and for ophthalmic angiography. The intraocular administration of indocyanine green is an off-label use of an FDA-approved product. It is used at concentrations of 0.125% to 0.5%, which at 270 milliosmols is slightly hypotonic to normal aqueous humor (about 290 milliosmols).[5,9] Indocyanine green must be reconstituted to an appropriate concentration each time it is used.

Fluorescein is approved by the FDA for IV administration for diagnostic fluorescein angioscopy or angiography of the fundus and of the iris vasculature. The intraocular administration of fluorescein is an off-label use of an FDA-approved product. The concentration of fluorescein used was not included in 2 reports[4,12] and was reported as 2% in a third.[7]

The FDA approved trypan blue in December 2004 specifically for use as an aid in ophthalmic surgery to stain the anterior capsule of the lens. Most reports on the use of this dye in ophthalmic surgery come from other countries, such as India[6,13] or The Netherlands.[14,15] These reports used concentrations of 1%,[6,13,16] 0.6%,[14] 0.1%,[15] and 0.06%.[6] Trypan blue has been commercially available outside the United States as Blurhex (trypan blue 0.1%, Pharma Ltd., Chennai, India) and is now available in the U.S. as VisionBlue (trypan blue 0.06%, D.O.R.C. International b.v., Zuidland, The Netherlands).

The FDA has not approved crystal violet for in vivo use. It is reported to have been used in 0.05% to 0.2% concentrations in a rabbit study.[17]

Neither has the FDA approved gentian violet for in vivo use. It is reported to have been used in 0.01% and 0.0001% concentrations in a rat and a human in vivo study.[18]

Questions for Assessment

This assessment addresses the following questions:

- Which dyes are effective in staining the capsule, and how do they compare with each other in effectiveness?
- Is capsule staining effective as an adjunct to cataract surgery?
- Is any dye safe as a staining agent, and at what concentration?

Description of Evidence

A Medline search of the peer-reviewed literature was conducted in March 2003 without date restrictions and was limited to articles published in English. The search also included the Cochrane Library of clinical trials. The terms used in these searches were *cataract extraction, phacoemulsification, dyes, staining and labeling, trypan blue, capsulorrhexis AC/drug effects, gentian violet, indocyanine green,* and *lens capsule, crystalline.* This search yielded 42 citations. An additional search conducted in May 2004 using the text words *mutagen* and *trypan blue* yielded 97 citations. Abstracts of meeting presentations are not subject to peer review and were not included in the analysis.

The panel reviewed the abstracts and selected 47 articles of possible clinical relevance for review. A review of the reference lists of these articles yielded an additional 11 citations that were retrieved in full text and reviewed for content relevance. Surveillance of major ophthalmic journals yielded 3 additional new articles that were reviewed for content relevance. Of these 61 articles, 36 were considered sufficiently clinically relevant for

evaluation by the panel methodologist, who used the following rating scale to assess the level of evidence provided in each article: a level I rating was assigned to properly conducted, well-designed, randomized clinical trials; a level II rating was assigned to well-designed cohort and case–control studies or poorly designed or conducted randomized controlled trials; and a level III rating was assigned to case series and case reports or poorly designed or conducted case–control and cohort studies.

No studies with level I evidence were found to address the issue of capsule staining as an adjunct to cataract surgery. There are 2 randomized controlled trials[13,19] that were assigned a level II evidence rating because of low power to detect differences between the groups (small numbers) and because of possible selection bias and ascertainment of outcome bias. The remaining reports are level III evidence. Articles that are expert opinions, describe experimental studies, or review articles were not rated. In general, published reports include few patients, and study reports lack detail. The issue of capsule staining has not received much systematic investigation, perhaps because the end point is completion of a surgical technique rather than a disease outcome.

Published Results

Which Dyes Are Effective in Staining the Capsule, and How Do They Compare to Each Other in Effectiveness?

There are no level I randomized clinical trials or level II high-quality cohort or case–control studies that can be used to answer this question about the effectiveness of dyes. A randomized dye study would necessarily be unmasked with visualization of the dye. Relevant data from level III case series and experimental studies have been evaluated and have taken into consideration the limitations implied by the lower grade of the evidence.

An animal study in porcine cadaver eyes found that crystal violet, light green, and trypan blue improved visualization of the capsule more than acid fuchsin, eosin Y, erythrosin Y, fluorescein, and phloxine B.[20] A preliminary in vitro study with unpublished data was described in which brilliant cresyl blue 1%, gentian violet 2%, methylene blue 5%, and trypan blue 0.1% stained the anterior capsule sufficiently to visualize the capsulorrhexis in the absence of a red reflex.[15] Other investigators used gentian violet 0.01% and 0.001% to stain rat and human anterior capsules. These authors concluded that gentian violet 0.01% provided good visualization of the anterior capsule; however, they provided no data in their nonrandomized comparative trial.[18] An in vitro study comparing trypan blue and fluorescein staining of anterior lens capsules found that 17% saturation was perceived by the surgeon as a good stain; this saturation level was reached after 1 minute with trypan blue and after 5 minutes with fluorescein.[21] The study also reported that fluorescein offered a satisfactory stain with a subcapsular application only and that prolonged exposure to trypan blue caused an intense stain that precluded the passage of white light.

Fluorescein was also compared with indocyanine green in the initial report on the use of indocyanine green for staining the lens capsule.[5] The authors reported that, in preliminary experiments in animal eyes, fluorescein stained the cornea, the entire lens, and the vitreous and, therefore, was not suitable for staining the anterior capsule.[5] In an expert opinion report by 2 surgeons on cadaver eyes comparing fluorescein sodium 2%, indocyanine green 0.5%, and trypan blue 0.1% and 2 staining techniques, under air and after subcapsular injection, the authors report that subcapsular injection of indocyanine green allowed the easiest recognition of the flap.[22] Generally, subcapsular injection resulted in more staining than instillation under air, and fluorescein resulted in less staining than did the other 2 agents. Of note, the authors reported that the "ability to perform technique" (i.e., complete a CCC) did not correlate with the degree of staining of the anterior capsule, suggesting that any staining is helpful.

It was reported in a single case that indocyanine green stained the anterior capsule but not the exposed cortex.[23] Trypan blue was also reported to have this property in a case series[14] and upon histological analysis.[24] A conflicting finding in a letter that reported a postmortem study of indocyanine green and trypan blue found that both dyes stained the cortex as well as the capsule but that staining patterns of the 2 tissues differed, allowing the necessary visual distinction.[25] It is not clear if the preferential staining of the capsule but not the cortex was a result of postmortem tissue changes or the technique of injecting under air rather than into the subcapsular space directly.

Another experimental study that was reported as expert opinion found that indocyanine green 0.5% and trypan blue 1% were effective in staining the posterior capsule for posterior CCC in human cadaver eyes.[26] Indocyanine green 0.5% was found to be useful in staining the posterior capsule for posterior CCC in 2 cases of cataract surgery in infants.[27] Trypan blue 0.1% also has been used for anterior and posterior capsule staining in infants.[13] A nonrandomized comparative trial of an increasing dilution of trypan blue found that a concentration as low as 0.0125% stained the anterior capsule.[11]

In summary, there is level III evidence that indocyanine green, trypan blue, and fluorescein are each effective in staining the capsule. There is also level III evidence that indocyanine green and trypan blue provide better ease of use and visualization of the capsule than fluorescein.

Is Capsule Staining Effective as an Adjunct to Cataract Surgery?

There is one level II study that addresses the question of whether capsule staining is effective as an adjunct to cataract surgery. Trypan blue 0.1% increased the frequency with which anterior and posterior CCC could be completed in pediatric cases, particularly in children who were under 5

years of age. Numbers were too small to demonstrate an advantage in children who were over 5.[13]

Trypan blue was also described as useful in cases of corneal opacities[16] and in cases of a lost leading edge[14] in a noncomparative case series (level III evidence). In the lost edge cases, trypan blue was instilled after the edge was lost; the dye stained the capsule but not the "exposed lenticular mass." According to a single report on the use of indocyanine green 0.5% in a case of traumatic white cataract with an anterior capsule tear, indocyanine green was reported to have this same affinity for the capsule but not the cortex.[23] The cataract was subsequently aspirated, leaving enough capsule support for a foldable IOL to be implanted in the ciliary sulcus.

A noncomparative case series (level III evidence) reported on the use of trypan blue in 52 cases of white cataract and found that 3.85% of cases were converted to an extracapsular cataract extraction (ECCE) due to an incomplete CCC.[3] The authors compared their results with those reported in another noncomparative case series. In this study, 212 patients with white cataracts underwent phacoemulsification without capsule staining, and the authors reported a rate of incomplete CCC of 28.3%.[28] However, in the case series in which no capsule staining was used, the authors reported a conversion to ECCE in 1.9% of cases.[28] It may be that this lower conversion rate to ECCE without dye was because the surgeon attempted to complete phacoemulsification despite an incomplete CCC and was successful in most cases. Another noncomparative case series (level III evidence) of 30 eyes found that trypan blue 0.1% seemed to facilitate the performance of a CCC in the absence of a red reflex, as it was successfully completed in all 30 cases.[15]

A nonrandomized comparative trial of indocyanine green versus no stain in mature cataracts found no advantage with staining[5]; however, with only 20 patients there was lower power to detect differences between groups (level II evidence). The outcomes that were measured related to toxicity and not to surgical advantage. This was also true of a trypan blue study in immature cataracts in which no advantage was reported (level II evidence).[19] Similarly, this may relate to the fact that the outcome measures were those of toxicity rather than surgical advantage.

A poorly controlled retrospective case–control study comparing phacoemulsification using indocyanine green with ECCE for advanced cataract found better postoperative visual acuity and less postoperative astigmatism in the phacoemulsification/indocyanine green group but more intraoperative complications. Patient populations were not equivalent, so these results are considered level III evidence.[29]

In an experimental study of 8 postmortem eyes, it was reported that indocyanine green 0.5% and trypan blue 0.1% were helpful in steps other than capsulorrhexis, as a hydrodissection/delineation agent. The resultant staining of the capsule and cortex improved visualization during phacoemulsification and the irrigation and aspiration steps.[30] A separate study reported the use of these 2 dyes at the same concentrations in a study of posterior CCC in 8 postmortem eyes.[26] The authors compared their results of 8 successfully completed posterior CCCs with a report of a 0.5% complication rate in attempts to perform posterior CCCs in a retrospective analysis of 650 patients in which the capsule was not stained.[31] The limited number of cases in which dye was used makes comparisons of successful completion rates between the 2 groups of doubtful value.

Of note, in one study designed to compare 3 dyes and 2 different staining techniques by 2 different surgeons, the authors reported that the "ability to perform technique" (i.e., complete a CCC) did not correlate with the degree of staining of the anterior capsule. In each permutation of the factors of surgeon, dye, and dye instillation technique, the surgeon rated ability to perform technique as easy, suggesting that any staining is helpful.[22]

A letter reported that trypan blue, with no concentration given, increased the rate of completion of CCC by trainees performing phacoemulsification surgery in immature cataracts.[32] Continuous curvilinear capsulorrhexis was completed in 10 of 10 cases in which capsule staining was performed and in only 3 of 10 cases in which staining was not performed.

In summary, there is level II and level III evidence that staining the capsule is helpful in completing capsulorrhexis, with the stronger evidence in pediatric cases of patients under 5 years of age and in cases of white cataract. The overall surgical advantage of a CCC completed with the use of dye has not been demonstrated, but this may be related to the outcome measures chosen rather than a failure to confer advantage.

Is Any Dye Safe as a Staining Agent, and at What Concentration?

One randomized controlled trial that addressed the question of whether any dye is safe as a staining agent was rated as level II evidence because of low power to detect differences between the groups. In this trial of trypan blue 0.06% applied under air in 25 patients with bilateral mature cataracts, the investigators found no evidence of endothelial damage induced by the intraoperative use of trypan blue for staining the anterior capsule. There was 7.5% endothelial cell loss in air and dye cases, versus 10.2% loss in air and no dye controls.[19] Although this report was supplied as a correspondence, it represents one of the few good studies of the use of dye in cataract surgery. In a noncomparative case series (level III evidence) of 25 cases of mature and hypermature cataract in which trypan blue 0.1% was used, mean endothelial cell loss was reported at 8.5% at 3 months,[33] which substantiates the data in the controlled study.

There are substantial data of lower evidence grade on the safety of trypan blue, typically in postmortem eyes or in patient studies conducted outside the U.S., because trypan blue was not approved by the FDA for in vivo use until 2004. Trypan blue was determined to be harmless as a vital stain to assess endothelium in donor cornea tissue.[34] A noncomparative case series (level III evidence) of patients who had trypan blue 0.1% instilled in the AC at the time of cataract surgery found no adverse effect after 8 years on endothelial cell counts or pachymetry in the 23 of 24 pa-

tients who had not died during that interval.[35] In 15 cases, the fellow eye was evaluated as a control.

Another noncomparative case series (level III evidence) of 30 eyes in which trypan blue 0.1% was used to facilitate capsulorrhexis found no adverse effect with follow-up of up to 12 months, but no endothelial counts or pachymetry was done preoperatively or postoperatively.[15] There is level II and level III evidence indicating that trypan blue 0.1% is not toxic to the cornea.

There are limited data suggesting that indocyanine green 0.125% to 0.5% is not toxic to anterior segment structures. A nonrandomized comparative trial of indocyanine green 0.5% versus no stain in 20 cases of white cataract found no difference between control (no dye) and experimental (indocyanine green) groups with respect to laser flare cell photometry, endothelial counts, and coefficient of variation (which corresponds to polymegathism). This suggests that in the short term in cases of mature cataract in which indocyanine green 0.5% is used to stain the anterior capsule, postoperative inflammation is not increased, and corneal endothelial cells are not affected.[5] With only 20 patients, this study had low power to detect differences between groups and was rated as level II evidence. In a separate study using 0.125% indocyanine green under viscoelastic rather than air, the technique of scanning laser ophthalmoscopy found the disappearance of fluorescence at a mean of 6 days (range, 2–9) in cases of phacoemulsification of mature cataracts. There did not seem to be remarkable loss of corneal endothelial cells or excessive inflammation (level III evidence).[9] In this study, the same concentration of indocyanine green was used to stain the internal limiting membrane for macular hole surgery, and fluorescence was observed for a mean of 2.7 months postoperatively. The investigators concluded that indocyanine green may be used safely in the anterior segment, but that longitudinal studies are required to reach conclusions about the safety of indocyanine green for posterior segment surgery.

Trypan blue, indocyanine green, and fluorescein all fall in FDA Pregnancy Category C for teratogenic effects. Trypan blue is labeled by the FDA as a mutagen in the Ames test[36] and a carcinogen in rats.[37] Trypan blue labeling states that it should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. Trypan blue is labeled as safe and effective for pediatric patients. Systemic exposure is likely to be exceedingly low if used as labeled.

Given known carcinogen and mutagen properties of trypan blue, a letter to the editor in 2002 that reviewed the literature and personal experience with dyes advised that trypan blue should be avoided in fertile/pregnant women and in children, due to possible teratogenic and/or mutagenic effects.[38] The authors commented that indocyanine green is a valuable alternative in these cases, although it is not clear why, because both dyes fall in FDA Pregnancy Category C. It is also worthwhile to note that, at the standard dose of 0.1%, trypan blue has been reported to cause permanent discoloration of a hydrophilic acrylic IOL, which required explantation.[39] In such cases, surgeons should choose indocyanine green or an alternative lens material. The IOL described in this report has never been marketed in the U.S.

The use of preservative-free fluorescein in the AC was assumed to be safe by the correspondents who reported its use for capsule staining.[4,12] The safety of fluorescein in the anterior segment has never been demonstrated.

Crystal violet used in an experimental rabbit study found that concentrations of 0.5% to 2% were damaging to the cornea and trabecular meshwork and that the concentration of 0.05% was not associated with damage.[17] Given that the lowest concentration is close to the concentration that is damaging, it seems inadvisable to recommend further use or study of crystal violet in humans.

Gentian violet 0.01% and 0.001% were used to stain rat and human anterior capsules in a nonrandomized comparative trial of these doses. The authors stated "that 0.01% and 0.001% solutions have no evident toxic effect that causes significant histopathological changes."[18] On postoperative day 1, the investigators noted mild corneal edema and an inflammatory reaction that improved at 1 week. They concluded that gentian violet at the concentrations used may lead to corneal edema.[18] It seems inadvisable to recommend further use or study of gentian violet in humans.

To summarize, there is level II and level III evidence that trypan blue is safe as a capsule stain in cataract surgery. There is no evidence that indocyanine green or fluorescein is harmful when used as reported as an adjunct to cataract surgery, but potential for toxicity, particularly in the long term, has not been evaluated fully for this off-label use. Potential toxicity in the event of inadvertent posterior segment exposure has not been evaluated fully for any of these agents. Crystal violet and gentian violet may be toxic at doses used for capsule staining and are not recommended.

Conclusions

There are data that confirm that dye is safe and effective as an adjunct for capsule visualization in cataract surgery. There are limited data suggesting that indocyanine green and trypan blue provide the best visualization and ease of use. The safety of indocyanine green at 0.125% to 0.5% in off-label use in the anterior segment has not been proven, although limited short-term studies indicate that there was no excessive inflammation or corneal toxicity. There are better data suggesting that trypan blue 0.1% is safe in the anterior segment. This agent has recently been approved by the FDA in a 0.06% formulation for in vivo use, and it does not require reconstitution involving dilution calculations.

There is evidence that the use of dye increases the rate of completed CCC in pediatric cases and in cases in which capsule visualization is difficult. Because most reports use safety measures rather than measures of surgical effectiveness, the advantage of dye-assisted phacoemulsification over alternative approaches to cataract surgery (such as phacoemulsification without the use of dye or ECCE) when capsule visualization is difficult is not well substantiated. It is reasonable to consider the use of dye in cataract surgery in cases in which inadequate capsule visualization or inexperience with capsule visualization may compromise the

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Original draft by:	Deborah S. Jacobs, MD	N
Ophthalmic Technology Assessment	Reginald G. Ariyasu, MD	N
Committee Anterior Segment Panel	Carol L. Karp, MD	N
	Michael D. Wagoner, MD	N
	Terry A. Cox, MD, PhD, Methodologist	N
Edited by:	Susan Garratt	N
Managing Editor:	Nancy Collins, RN, MPH	N
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Category	Abbreviation	Specific Financial Interests
Product	P	Financial interest in equipment, process, or product presented.
	Pc	Such interest in potentially *competing* equipment, process, or product.
Investor	I	Financial interest in a company or companies supplying the equipment, process, or product presented.
	Ic	Such interest in a potentially *competing* company.
Consultant	C_	Compensation received within the past 3 years for consulting services regarding the equipment, process, or product presented.
	Cc_	Such compensation received for consulting services regarding potentially *competing* equipment, process, or product.
		Examples of compensation received include:
	C1 or Cc1	1. Retainer
	C2 or Cc2	2. Contract payments for research performed
	C3 or Cc3	3. Ad hoc consulting fees
	C4 or Cc4	4. Substantial nonmonetary perquisites
	C5 or Cc5	5. Contribution to research or research funds
	C6 or Cc6	6. Contribution to travel funds
	C7 or Cc7	7. Reimbursement of travel expenses for presentation at meetings or courses
	C8 or Cc8	8. Reimbursement of travel expenses for periods of direct consultation
None	N	No financial interest. May be stated when such interests might falsely be suspected.

outcome. The use of dye in routine cases cannot be recommended until a lack of toxicity is more clearly demonstrated in the event of longer duration exposure or posterior segment exposure.

Future Research

More studies are needed to confirm the lack of toxicity of indocyanine green and trypan blue, particularly in the event of posterior segment exposure or longer duration exposure. The use of dye as an adjunct to cataract surgery was widespread in the United States even before FDA approval of trypan blue for that purpose. It is thus unlikely that a randomized trial to demonstrate the effectiveness of dye-enhanced cataract surgery will ever be undertaken. With the ongoing use of these dyes, continued retrospective analysis of their impact on surgical outcome is warranted. Assessment of off-label and no-label usage of drugs, devices, and other adjuncts to eye surgery, such as indocyanine green and trypan blue, remains a challenge because of the lack of randomized clinical trials that typically accompany the introduction of this type of technological innovation into surgical practice.

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