

A Comparison of the Laser Flare Cell Meter and Fluorophotometry in Assessment of the Blood-Aqueous Barrier

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Purpose. To evaluate and compare the use of the Kowa laser flare cell meter and intravenous anterior chamber fluorophotometry in assessment of the blood-aqueous barrier after cataract surgery.

Method. Laser flare and cell measurements and fluorophotometry were performed at 1 and 3 months after surgery in 48 eyes of 44 patients admitted for routine cataract surgery. The fellow pseudophakic eyes of these patients were used as controls.

Results. The two techniques measure different parameters, but both methods are able to document the integrity or breakdown of the blood-aqueous barrier. However, the laser flare cell meter is more sensitive in quantifying subtle changes in barrier function to large molecules (proteins). Various methods of assessing anterior chamber fluorophotometry data were also compared. Measurement of a diffusion coefficient (requiring the measurement of plasma fluorescence) was not found to be more sensitive than other methods and did not alter the clinical significance of data obtained from the measurement of anterior chamber fluorescence alone.

Conclusions. Both the laser flare cell meter and fluorophotometry provide a method for the assessment of the postoperative blood-aqueous barrier. However, the laser flare cell meter is rapid, noninvasive, and relatively easier to use. Therefore, for clinical use, it has great practical advantages over fluorophotometry. *Invest Ophthalmol Vis Sci.* 1993;34:3124–3130.

Quantification of changes in the blood-aqueous barrier (BAB) play an important role in the understanding of the physiology of the anterior chamber, the assessment of anti-inflammatory drugs, the study of the effects of anterior segment surgery and its complications, and the management of uveitic disease. Until recently, it was only possible to measure changes in the BAB by anterior segment fluorophotometry, which is invasive, time consuming, and carries a small risk of severe allergic reactions.¹ Noninvasive methods for the measurement of aqueous flare have been described by others, but because these instruments are not commercially available, their clinical use has been limited.^{2–4} The Kowa Laser Flare Cell Meter (Kowa Acculas, San Jose, CA) is a recently introduced instru-

ment that allows quantification of aqueous flare and cells by measurement of scattered light with the great advantages of rapidity, noninvasiveness, and simplicity of operation.⁵ To date, there has been no published comparative study of these two techniques. Our aim has been to compare both techniques in the assessment of changes in the BAB that occur after cataract surgery.

Previous fluorophotometric studies have used a variety of parameters to assess the BAB such as diffusion or permeability coefficients of varying complexity,^{6,7} measurements of peak anterior chamber (AC) fluorescence,^{8,9} the ratio of AC fluorescence between fellow eyes,^{10,11} or the ratio of sequential readings.¹² Recently, there has been agreement by the European Economic Community working party on ocular fluorophotometry that AC fluorophotometry should be assessed by a diffusion coefficient, and the technique for this has been standardized.¹³ This study has also provided an opportunity to assess the various methods of determining BAB function by AC fluorophotometry and their relative merits.

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MATERIALS AND METHODS

Patients

Forty-eight eyes of 44 patients (mean age, 68.6 years; range, 40 to 80 years; 17 men, 27 women) admitted for routine cataract surgery were selected for inclusion in the study. Each patient was systemically well and, in particular, had no cardiovascular or respiratory contraindications to intravenous fluorophotometry. All patients were free of other ocular disease and, in particular, were taking no systemic anti-inflammatory medication. The informed consent of each patient was obtained, and the study was conducted according to the tenets of the Declaration of Helsinki. Ethical approval for the study was given by the West Lambeth Health Authority. All patients underwent routine endocapsular surgery performed by a single surgeon with a standardized procedure of in the bag all PMMA intraocular lens insertion with the use of viscoelastic material through a limbal incision. All patients received a standardized postoperative medication regime (unless clinically contraindicated) consisting of topical dexamethasone 0.1% and neomycin 0.35% four times daily for the first week and then twice daily for a three more weeks.

TECHNIQUES

Fluorophotometry

Fluorophotometry was performed using a Fluorotron Master (Coherent Radiation Inc., Palo Alto, CA) with intravenous 20% sodium fluorescein at a dose of 14 mg/kg according to the recommended protocol of the European Economic Community working party on ocular fluorophotometry.¹³ Briefly, fluorophotometric scans were performed on both eyes along the optical axis from the retina to the cornea using the posterior segment program. These were performed before injection and at 60 minutes after injection. Plasma samples were taken at 7, 15, and 55 minutes after injection. All plasma samples were frozen for later processing in batches. The peak concentration of fluorescence in the anterior chamber (ng/ml) at 60 minutes (Ca) was derived from the scans. The free fluorescein plasma concentration (nonprotein bound fluorescein) was measured on the fluorophotometer using a plasma ultrafiltrate (diluted 1 in 200 in phosphate buffer, pH = 7.4) prepared by centrifugation through a filter (MPS-1 filters, Amicon, New York, NY).¹³ The integral of the nonprotein bound fluorescein concentration (B) was determined using dedicated software provided with the Fluorotron Master. The results of fluorophotometry were then expressed as a diffusion coefficient (Kd) using the following formula¹³:

$$Kd = Ca/B$$

Laser Flare Cell Meter

The Kowa Laser Flare Cell Meter allows quantification of aqueous flare and cells by measurement of light scattering of a helium-neon laser beam within the anterior chamber.^{5,14} The instrument consists of three main components, a helium-neon laser slit lamp, a binocular microscope fitted with a photomultiplier tube, and a personal computer. The He-Ne beam is projected into the anterior chamber, and scattered light from within a sampling window is detected by the highly sensitive photomultiplier tube. This scattered light is then analyzed by the instrument to produce an aqueous flare value expressed in photons/ms. Each scan takes 1 second. To avoid the introduction of bias, five sequential scans were accepted and averaged provided that the background scatter was less than 15% on each individual scan.

Fluorophotometry and laser flare and cell measurements were performed on the same day on both eyes of each patient at both 1 and 3 months after surgery. It was not possible to obtain laser flare measurements on the fellow eye of one patient because of corneal opacification.

Control Eyes

There are difficulties in selecting normal eyes to establish a normal range for fluorophotometry because of autofluorescence of the lens particularly, as is often the case in clinical studies, when this has cataractous changes. Using the Fluorotron anterior segment adaptor, cataractous lens autofluorescence can spread forward into the AC making it difficult to obtain an accurate pre-injection baseline measurement. The European Economic Community protocol for standardization of fluorophotometry recommends use of the posterior segment program because this allows simultaneous measurement of blood-retinal and blood-aqueous barriers. With the posterior segment program lens autofluorescence cannot be separated from AC fluorescence after injection, and minor degrees of misalignment between the preinjection and postinjection scans could therefore lead to error in the derivation of absolute values. To avoid these problems, we chose to take those fellow eyes that had had uneventful pseudophakic surgery more than 1 year earlier. These eyes have no autofluorescence from the implant, and anterior chamber fluorescence postinjection is uncontaminated by any artifact. Although these problems do not apply to flare measurements, we used the same eyes to establish the normal range of flare. Thirteen patients had entirely normal, healthy, pseudophakic fellow eyes with surgery more than 1 year earlier and met the criteria for inclusion in the "normal" control group.

Statistical Analysis

Initial examination of the data showed that all the data were highly positively skewed. The flare values were approximately normally distributed after logarithmic transformation, but the fluorophotometry data were not. Therefore, for consistency, nonparametric tests were used for all data analysis. All variables are presented as median values with 95% confidence intervals.¹⁵ Differences in aqueous flare, AC fluorescence, and diffusion coefficients between groups (operated and control eyes) were analyzed using the Mann-Whitney test. Changes in aqueous flare, AC fluorescence, and diffusion coefficients within groups between 1 and 3 months after surgery were analyzed using the Wilcoxon test for paired data. Relationships between aqueous flare, AC fluorescence, and diffusion coefficients were compared using Spearman's rank correlation coefficient. An assessment of the reproducibility of laser flare measurements and fluorophotometry was obtained by a comparison of values in the control eyes at 1 month and 3 months after surgery. The variability in these parameters between the two visits was assessed using the formula

$$\frac{|x_2 - x_1|}{(x_1 + x_2)/2} \times 100\%$$

where x_1 and x_2 are the first and second measurements, respectively. P values < 0.05 were considered statistically significant. All flare values are expressed as photons/ms, anterior chamber fluorescence as ng/ml equivalence to free fluorescein, and diffusion coefficients as 10^{-4} /min.

RESULTS

Reproducibility/Short-Term Variability

The variability in the control eyes between 1 and 3 months was 17.6 (4.4% to 45.7)% (median difference 1.2, 0.4, to 3.8 photons/ms) for aqueous flare, 29.8 (17.5% to 37.5)% (median difference 42.3, 29.5 to 71.5 ng/ml) for AC fluorescence, and 39.8 (13.5% to 52.2)% (median difference 0.6, 0.3 to 1.3×10^{-4} /min) for diffusion coefficient.

Control Eyes

There was no significant difference ($P = 0.9$) in aqueous flare value at 1 month after surgery between the 13 control eyes (median 8.6, 95% CI 6.2 to 12.5) and the entire group of 47 fellow eyes (8.6, 7.3 to 9.5), indicating that the 13 control eyes were representative of the entire group and that the selection criteria for the fellow eyes had not introduced any bias.

Aqueous Flare

Aqueous flare (Table 1) in the operated eyes was significantly higher than in the control eyes at both 1 ($P = 0.0012$) and 3 months ($P = 0.002$) after surgery. The decrease in aqueous flare in the operated eyes between 1 and 3 months was highly statistically significant ($P = 0.0001$). Over the same time period, there was also a small median decrease in flare in the control group of eyes of 1.2 (-3.8 to $+0.6$) photons/ms ($P = 0.03$, $n = 13$).

Diffusion Coefficient

The diffusion coefficient (Table 1) in the operated eyes was significantly higher than in the control group of eyes at both 1 ($P = 0.003$) and 3 months ($P = 0.007$) after surgery. There was no statistically significant change in diffusion coefficient between 1 and 3 months in either the operated group of eyes ($P = 0.7$) or the control group of eyes ($P = 0.07$).

Anterior Chamber Fluorescence at 60 Minutes

The mean 60-minute AC fluorescein concentration (Table 1) in the operated eyes was significantly higher than in the control eyes at both 1 ($P = 0.004$) and 3 months ($P = 0.03$) after surgery. There was a significant decrease in AC fluorescence between 1 and 3 months in the operated eyes ($P = 0.02$), but there was no significant change in the control group of eyes ($P = 0.10$).

Ratios of Aqueous Flare, Diffusion Coefficient, and AC Fluorescence Between the Operated and Fellow Control Eye

A ratio for aqueous flare, diffusion coefficient, and AC fluorescence between the operated eye and its fellow eye was calculated for the 13 treated eyes for which a control eye was available. The median ratio for aqueous flare between the operated eyes and the fellow eyes decreased from 1.8 at 1 month after surgery to 1.4 at 3 months ($P = 0.03$). Although the diffusion coefficient ratio decreased from 1.4 at 1 month to 1.2 at 3 months, and the ratio of 60-minute AC fluorescence decreased from 1.4 to 1.2 over the same time period, these changes were not statistically significant ($P = 0.06$ for both).

Correlation of Aqueous Flare and Diffusion Coefficient

At both 1 and 3 months after surgery, there was a statistically significant correlation ($r = 0.48$, $P = 0.0006$ at 1 month, and $r = 0.50$, $P = 0.0003$ at 3 months) between aqueous flare and anterior chamber fluorescence in the operated eye (Figs. 1 and 2). A similar statistically significant correlation ($r = 0.43$, $P = 0.002$ at 1 month, $r = 0.50$, $P = 0.0003$ at 3 months)

TABLE 1. A Comparison of Aqueous Flare, Diffusion Coefficient, and A-C Fluorescence in Operated ($n = 48$) and Fellow Eyes ($n = 13$) at 1 and 3 Months After Cataract Surgery

	<i>1 Month</i>	<i>3 Months</i>	<i>P Value</i>
	<i>Median</i> <i>(94% CI)</i>	<i>Median</i> <i>(95% CI)</i>	<i>Change</i> <i>1–3 months</i>
Flare (photons/ms)			
Operated Eye	13.7 (11.7–17.9)	9.6 (9.6–11.6)	0.0001
Control Eye	8.6 (6.2–12.5)	6.8 (5.1–9.2)	0.03
<i>P Value</i> (operated vs control)	0.0012	0.002	—
Ratio			
Operated: Control Eye	1.8 (1.3–3.3)	1.4 (1.1–1.8)	0.03
Diffusion Coefficient (10^{-4} /min)			
Operated Eye	3.6 (2.7–4.8)	3.6 (2.7–4.9)	0.70
Control Eye	1.9 (1.3–2.9)	2.1 (1.4–3.9)	0.07
<i>P Value</i> (operated vs control)	0.003	0.007	—
Ratio			
Operated: Control Eye	1.4 (0.9–2.9)	1.2 (1.0–1.5)	0.06
AC Fluorescence (ng/ml)			
Operated Eye	252.8 (200.5–345.8)	237.2 (189.8–313.8)	0.02
Control Eye	122.7 (111.0–216.1)	159.8 (92.9–255.9)	0.10
<i>P Value</i> (operated vs control)	0.004	0.03	—
Ratio			
Operated: Control Eye	1.4 (0.9–3.0)	1.2 (1.0–1.5)	0.06

CI = confidence interval.

was found to exist between aqueous flare and the diffusion coefficient.

There was no statistically significant correlation between aqueous flare and AC fluorescence or diffusion coefficient in the control group of eyes at either 1 or 3 months after surgery ($P > 0.05$).

Correlation of AC Fluorescence and Diffusion Coefficient

There was a highly significant linear correlation between AC fluorescence and the diffusion coefficient at both 1 ($r = 0.81$, $P = 0.0001$) and 3 months ($r = 0.90$, $P = 0.0001$) after surgery.

DISCUSSION

Assessment of BAB function by fluorophotometry is a time honored technique but has the practical problems of the administration of a potentially hazardous drug,¹ a lengthy test, and the inability to perform rapid sequential studies. This is compounded by complicated pharmacokinetics and, until recently, a lack of consensus on the technique and the interpretation of the data. Sodium fluorescein when systemically administered is rapidly bound to plasma albumin and

also metabolized to glucuronide.¹⁶ These compounds have different molar fluorescence, polarity, and diffusion coefficients both in and out of the eye.^{17,18} Furthermore, free fluorescein fluorescence in the AC can be quenched by in situ protein.¹⁹ Thus, a measurement of anterior chamber fluorescence, although expressed by the fluorophotometer as equivalence to free fluorescein, is in fact a measurement reflecting the composite fluorescence of sodium fluorescein, protein bound fluorescein, and fluorescein glucuronide (with 30% to 40% and 4% to 5% of fluorescence relative to free fluorescein, respectively). The proportional contribution of these compounds cannot easily be separated and in sequential studies of pathologic eyes is likely to vary from time to time depending on the state of the blood-aqueous barrier. The simplest way to interpret fluorophotometry data is to measure the 60-minute AC fluorescence when AC fluorescence is almost at its peak.^{8,9} Other authors have used ratios of operated-to-fellow eye^{10,11} or sequential ratios after surgery.¹² Although ratios may compensate for variations in technique, the use of a ratio between the operated eye and its fellow eye is not always possible because the unoperated eye may not be normal (e.g.,

recent surgery or lens opacities). To overcome this and to allow for comparison between patients, other investigators have measured either a permeability or a diffusion coefficient of varying complexity. These require the measurement of plasma fluorescein and hence are more expensive, time consuming, and less acceptable to the patient. Many of these calculations make assumptions not always applicable in the pathologic eye (e.g., a standard AC volume, and aqueous and plasma have the same proportion of fluorescent metabolites). In addition, processing of plasma specimens can produce further variables and meticulous care must be taken when storing specimens, dilutions, filters, and calibration of the fluorophotometer. To standardize the use of fluorophotometry, a European Economic Community working party has defined and recommended the use of a diffusion coefficient with a specific technique.¹³ We have used this as the standard by which to compare the other fluorophotometric techniques.

The laser flare cell meter has great practical advantages over fluorophotometry. It is rapid, noninvasive, requires minimal patient cooperation, and can be repeated within minutes to demonstrate dynamic changes. There is a highly significant linear relationship between laser flare values and protein concentration both *in vitro*^{5,14} and *in vivo*,²⁰ and the reproducibility of measurements of aqueous flare has been found to be 8.26% on measurements repeated within 5 minutes and 12.2% on measurements taken 1 week apart.¹⁴

The selection of control eyes for this study was rigorous and produced a lower mean level of AC fluorescence with lower standard deviations than those reported on in an earlier study by Ferguson et al,⁹ who, using an identical technique, found a mean AC fluores-

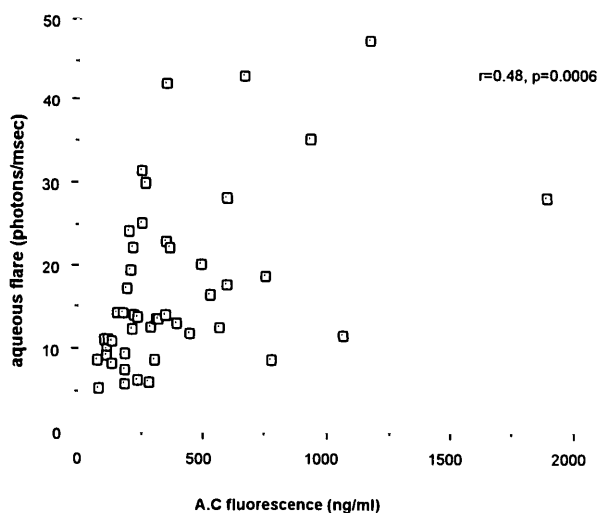


FIGURE 1. Correlation of aqueous flare and AC fluorescence at 1 month after cataract surgery.

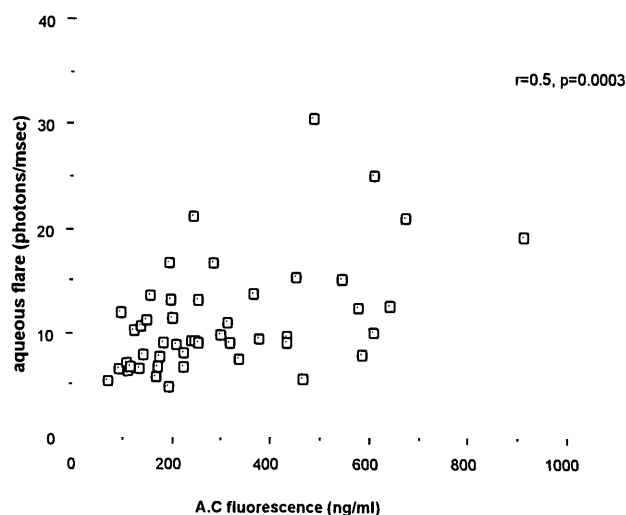


FIGURE 2. Correlation of aqueous flare and AC fluorescence at 3 months after cataract surgery.

cence in normal eyes of 301 ng/ml (SD \pm 108 ng/ml). Flare values are much less affected by the presence of a cataractous lens (unpublished observations, 1991), and, although there is a diurnal variation in aqueous flare in normal eyes, this is small and not significant within the working day.¹³ There was no significant difference between the flare values in the 13 control eyes at 1 month after surgery and in the entire group of 47 fellow eyes. Furthermore, the mean flare value in our control group is comparable to the previously reported values for an age-matched group of normal eyes (5.3 ± 1.1 (mean \pm SD) in healthy subjects aged 61 to 70 years and 6.5 ± 1.2 in subjects over 70 years of age).¹⁴ We think this supports our conclusion that the control eyes used in this study are representative and their selection has not introduced a bias.

In our study we found that aqueous flare, as measured by the laser flare cell meter, and leakage of fluorescein into the AC, as measured by fluorophotometry, are both significantly elevated at 1 and 3 months after cataract surgery. Several other fluorophotometric studies have found that recovery of the BAB has usually occurred by 3 months after surgery.^{9,10,21} This difference may reflect our stricter criteria for the definition of a fellow eye as "normal." The use of either 60-minute AC fluorescence, the diffusion coefficient, or ratios produced the same conclusion. Ratios (between operated and fellow eyes) obtained by fluorophotometry were almost identical irrespective of whether anterior chamber fluorescence or the diffusion coefficient was used. There was also a highly significant correlation between anterior chamber fluorescence and diffusion coefficient. These results are of great practical importance because they suggest that in systemically healthy patients there is no special advantage in any particular method of fluorophotome-

tric data interpretation. The diffusion coefficient relates the transfer of fluorescein into the AC to its plasma concentration and therefore might have advantages in allowing a comparison with the results of other studies or between individuals given different doses of fluorescein by different routes (intravenous or oral). Nonetheless, for an individual clinical study, measurement of a diffusion coefficient has no fundamental advantage over AC fluorescence provided that the patients are systemically well and are given the same dose of fluorescein by the same route.

We found a statistically significant correlation between the laser flare cell meter and fluorophotometry in pathologic eyes postoperatively, but the linear regression accounted for only between 17% to 28% of the variance (Figs. 1 and 2). Therefore, despite a correlation between the two parameters, the nature of the relationship is not clear. This would seem to imply that the two techniques are measuring different and not identical parameters of BAB function. This conclusion is supported by the changes in aqueous flare and fluorophotometry between 1 and 3 months after surgery. Although there was a statistically significant decrease in aqueous flare between 1 and 3 months, no change in the diffusion coefficient could be shown to occur over the same time period. This appears to demonstrate that aqueous flare is a more useful indicator of sequential changes in BAB function than fluorophotometry. However, the clinical significance and relevance of this difference remains to be determined. One might have expected that fluorophotometry, which measures the presence of a small molecular weight substance, might have been more sensitive than the laser flare cell meter.

The lack of a linear relationship between the two techniques and the apparent greater sensitivity of the laser flare cell meter can be explained by the different principles of measurement used by the two techniques. The laser flare cell meter produces an aqueous flare value by analysis of the intensity of light scattering by protein in solution in the anterior chamber. There is a linear relationship between the intensity of light scattering and protein concentration. However, light scattering is not only dependent on protein concentration but also on molecular size (a larger molecular size producing greater light scattering).² Thus, two protein solutions of the same concentration but different molecular weights will have different laser flare values. As the BAB recovers, there is a reduction in the apparent pore diameter of the barrier resulting not only in a decrease in protein concentration in the AC but also in a relative reduction in higher molecular weight proteins.²² These changes would be expected to have a relatively greater effect on light scattering than on the AC concentration of a small molecule such as fluorescein, which will not be so sensitive to changes

in pore size above a certain threshold value. Fluorophotometry is therefore useful in documenting the integrity or breakdown of the BAB, but the laser flare cell meter appears to be more sensitive in quantifying more subtle changes in barrier function to protein molecules. The two techniques measure BAB function using different tracers, and the choice of instrument will depend on whether one is interested in measuring barrier function to protein molecules (laser flare) or to the influx of a small molecule such as fluorescein or a drug (fluorophotometry), although in the pathologic eye a proportion of AC fluorescence is also derived from the binding of fluorescein to plasma or aqueous protein.^{18,19}

There was a poor correlation between the laser flare cell meter and fluorophotometry in the normal eye with an intact BAB. It has been shown in previous studies that laser flare measurements are highly reproducible at low levels of protein found in the normal eye and that there is a highly significant linear correlation between laser flare values and protein concentration *in vitro*.¹⁴ This poor correlation may reflect the low levels of protein and leakage found in the normal eye together with the variability of the methods of measurement. In this comparative study, the variability of the parameters measured in the control eyes over the 2-month interval was 17.6% for aqueous flare (a median difference of only 1.2 photons/ms), which compares favorably with a variability of 29.8% for 60-minute AC fluorescence and 39.8% for the diffusion coefficient. A previous study on normal eyes has shown there was no significant difference between flare measurements repeated after an interval of 1 week and that the variability over this period, expressed in the same way as in the present study, was 13.3%.¹⁴ Such an analysis of reproducibility assumes that there is no other change in the underlying state of the eye and the parameter being measured between the two measurements. Although this was statistically true for the results of fluorophotometry, there was a small but significant decrease in aqueous flare in the control eyes over this period that may represent a consensual response to implant surgery.¹² The higher variability in aqueous flare found in this study may be explained by this consensual response as well as the much longer interval between the two measurements.

In conclusion, although the two techniques do not measure identical parameters, both appear to be able to provide a measure of postoperative inflammation and both are of use in the quantitative assessment of postoperative damage to the BAB. The laser flare cell meter is, however, more sensitive in demonstrating changes of the BAB in the pseudophakic eye and in studies in the physiologic eye. This, together with its great practical advantages, means that it is likely to supersede anterior segment fluorophotometry for this

purpose. Measurement of plasma fluorescence and calculation of a diffusion coefficient does not improve the clinical accuracy of AC fluorophotometry.

Key Words

laser flare meter, blood-aqueous barrier, fluorophotometry, aqueous proteins, cataract surgery

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