CORRESPONDENCE

Sir,
Hydroxychloroquine and the eye: an old unsolved problem

We agreed with the conclusions of Latasiewicz *et al*[1] 'Hydroxychloroquine retinopathy: an emerging problem', which cited cases of hydroxychloroquine (HCQ)-induced retinal damage. Three patients had received 400 mg HCQ daily for over 15 years (equaling 4.93 mg/kg/day in two and 5.6 mg/kg/day in one) and all developed maculopathies of varying severity. The study by Latasiewicz *et al*[1] recommended a standardized screening protocol to monitor for retinal toxicity in patients treated with HCQ. Ocular toxicity ranged from non-significant keratopathy to a potentially blinding retinopathy as described previously with varying doses of HCQ.[1,2] In 2016 the American Academy of Ophthalmology recommended a maximum daily HCQ use of 5.0 mg/kg, a baseline fundal examination to exclude pre-existing maculopathy and an annual screening after 5 years of HCQ use.[3]

Being a synthetic antimalarial, HCQ is used for immunomodulation in autoimmune diseases.[2] Commonly used daily doses of HCQ are 200mg or 400 mg (which equals a dose of 5.3 mg/kg and 2.6 mg/kg for a 75 kg patient, respectively), and therapeutic plasma concentrations of 500–2000 ng HCQ/ml have previously been described.

The pathogenesis of HCQ-induced retinal toxicity is not fully understood. HCQ displays a high affinity to melanin containing cells in the skin, ciliary bodies, and retinal pigment epithelium (RPE).[2] Previous *in vitro* studies on cultured RPE cells suggest that HCQ causes retinal damage through changing RPE lysosomal pH, resulting in higher levels of lipofuscin, a pigment that commonly accumulates with age and is associated with photoreceptor degeneration.[2] Interestingly Bharadwaj *et al*[4] showed *in vitro* that leukocyte migration on retinal epithelium is linked to an increased expression of adhesion molecules (including intercellular adhesion molecule (ICAM-1)).

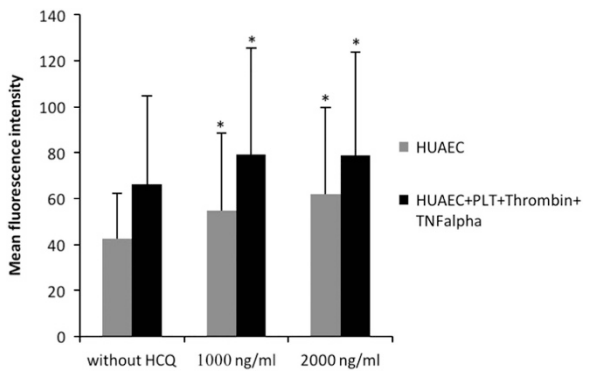

Figure 1 Surface expression of ICAM-1 on HUAEC with and without 24 h pre-incubation with 1000ng/ml or 2000 ng/ml HCQ. $N=7$; PLT, platelets; TNFalpha, tumor necrosis factor alpha (*$P<0.05$, as evaluated by Dunnett's test).

Our *in vitro* experiments are the first to link therapeutic levels of HCQ to increased ICAM-1 expression. In this model, HCQ-exposed human umbilical arterial endothelial cells are stimulated with tumor necrosis factor alpha and thrombin-activated platelets, and showed significantly elevated levels of ICAM-1 when HCQ doses of >1000 ng/ml are used (Figure 1). These results suggest that ICAM-1 may be involved in the pathogenesis of HCQ-induced retinal toxicity.

Conflict of interest

The authors declare no conflict of interest.

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Sir,
Are techniques for general anesthesia less invasive than procedures for cataract surgery?

We read with special interest the retrospective cohort study by Alboim *et al*[1] who examined the importance of preoperative evaluation for outpatients undergoing cataract surgery. They suggested that preoperative evaluation has no role in reducing adverse events in these

patients. On the other hand, their study showed that 36 in 240 preoperatively evaluated patients were managed for optimization before surgery, where reversal for anticoagulation was done for 18.7% patients. In twelve emergency hospital visits after surgery, one adverse event concerning anticoagulation was included.

Because of the minimum invasiveness of cataract surgery, a consensus that direct oral anticoagulants (DOACs) as well as vitamin K antagonists (VKAs) should be continued around the time of the procedure is steadily growing.[2] Clinically available blood-test monitoring cannot exactly measure the anticoagulation functions of DOACs.[3] This is also leading to a practical trend that DOACs can be used without the need for routine monitoring. We have recently surveyed 728 sequential clinical records of patients undergoing cataract surgery in our hospital after the approval of the institutional review board. We found that DOACs were prescribed to 12 patients, while only one patient with dabigatran was preoperatively evaluated for coagulopathy. Out of 42 patients taking warfarin 23 were not monitored with PT-INR. It is noteworthy that PT or APTT longer than normal limits in patients taking DOACs is a sign of the overdosing of DOACs.[3] PT-INR > 3 in patents with VKAs also points to abnormal bleeding.[2,4]

In this context, we think of a scenario where an anesthetic plan for outpatient cataract surgery was unexpectedly changed from local to general anesthesia. If this patient had taken DOACs several hours before the surgery, the risk of hematoma in the upper airway caused by laryngoscopy should be increased.[4] If the patient had renal dysfunction, this risk should be more increased.[3] If this patient had taken VKAs for several days before surgery, but not monitored with PT-INR, such risk should also be increased. Considering such a scenario, we recommend to monitor coagulation functions before cataract surgery when omitting the preoperative evaluation.

Conflict of interest

The authors declare no conflict of interest.

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Sir,
Increased corneal densitometry as a subclinical corneal change associated with multiple myeloma

Multiple myeloma (MM) is a malignant plasma cell disorder of the bone marrow characterized by high levels of monoclonal serum protein and multiple organ involvement.[1] Corneal crystalline deposition is a rarely reported but known ocular manifestation of MM.[2] Recent reports have employed *in vivo* confocal microscopy (IVCM) to investigate MM-associated crystalline deposits.[3–5] However, the pathophysiology of this condition is not fully understood. To objectively quantify the MM-associated corneal changes in differing depths of the cornea, we obtained corneal densitometry data in MM patients using a Scheimpflug camera. A hypothesis for the pathogenesis of this condition is discussed.

Ten MM patients (5 males; 5 females; mean age, 70.1 ± 6.1 years) who were being routinely examined for their systemic disease were referred to the Ophthalmology department from the Hematology department. All patients underwent ophthalmologic screening, including slit-lamp and fundus examination. All eyes were deemed to be clear by slit-lamp examination without abnormal findings. Corneal densitometry measurements from the anterior, central, and posterior cornea within a 6-mm-diameter were attained using a Scheimpflug camera (Pentacam HR; Oculus GmbH). In total, 20 eyes from 10 MM patients were enrolled in this prospective case series. Ten eyes of 10 age-matched patients (mean age, 66.9 ± 6.5 years) undergoing routine examination before cataract surgery served as controls. Table 1 shows the densitometry values of the central 2-mm zone and of the surrounding 2- to 6-mm zone

Table 1 Subclinical corneal densitometry changes in anterior, central, and posterior corneal layers

Corneal densitometry (scatter units)	*Control group (10 eyes)*	*Multiple myeloma group (20 eyes)*
Anterior (0–2 mm)	23.43 ± 1.50	29.57 ± 2.43[a]
Anterior (2–6 mm)	22.42 ± 1.81	29.06 ± 3.51[a]
Central (0–2 mm)	14.68 ± 0.71	18.54 ± 2.40[a]
Central (2–6 mm)	14.26 ± 0.92	18.51 ± 2.23[a]
Posterior (0–2 mm)	12.93 ± 0.93	13.34 ± 1.55
Posterior (2–6 mm)	13.08 ± 1.28	14.07 ± 1.65

[a] $P < 0.001$ for control group *vs* multiple myeloma group.
Data are expressed as the mean ± SD.
0–2 mm: Central 2-mm diameter zone.
2–6 mm: The annulus extension zone (ie, the ring within a 2–6-mm diameter).