

Transient vacuolar changes of the crystalline lens in patients using a dispersive ophthalmic viscosurgical device

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Abstract

• **AIM:** To report the clinical prognosis and pathological findings of accidental lens vacuolar changes in eyes with intraoperative exposure to a dispersive ophthalmic viscosurgical device (OVD).

• **METHODS:** Two patients who developed transient lens vacuolar changes during uneventful persistent pupillary membrane (PPM) removal surgery were presented and followed up. This event was speculated to be associated with an intraoperative dispersive OVD DisCoVisc (hyaluronic acid 1.6%-chondroitin sulfate 4.0%) exposure. Then, to provide the pathological basis for our speculation, another four cataract patients were randomly exposed to different OVDs, and their anterior lens capsules were investigated with transmission electron microscopy (TEM).

• **RESULTS:** After months, the subcapsular vacuoles in both PPM cases were gradually disappeared without visual deterioration. For the cataract patients, similar lens changes were observed intraoperatively in those exposed to a dispersive DisCoVisc but not a cohesive OVD IVIZ (sodium hyaluronate gel 1.0%). In addition, marked ultrastructural changes, including chromatin condensation, extensive cytoplasmic vacuoles, and obvious intercellular space between lens epithelial cells in the anterior lens capsules of all eyes exposed to DisCoVisc, were observed by TEM.

• **CONCLUSION:** The lens vacuolar changes may be associated with a dispersive OVD exposure. Therefore,

it is not preferable to use dispersive OVDs in patients with transparent lenses or without the intention of lens extraction. In addition, close follow-ups instead of immediate lens extraction are recommended for the occurrence of similar lens lesions.

• **KEYWORDS:** vacuolar change; crystalline lens; ophthalmic viscosurgical devices; lens epithelial cells; transmission electron microscopy

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INTRODUCTION

Ophthalmic viscosurgical devices (OVDs) have become an essential tool in ocular surgery, especially in anterior segment surgery. There are several OVDs available on the market, including cohesive OVDs, dispersive OVDs, viscoadaptive OVDs and a combination of OVDs or dual viscoelastic systems^[1]. Thereinto, DisCoVisc (hyaluronic acid 1.6%-chondroitin sulfate 4.0%), regarded as a special dispersive OVD, has an intermediate cohesive/dispersive index and owns mixed properties of dispersive and cohesive OVDs^[2]. In surgical terms, this would mean good retention during surgery like a dispersive OVD and easy removal after surgery like a cohesive OVD, facilitating both space maintenance and tissue protection. These multiple features enable them to facilitate the ocular surgery, such as lens surgery^[3-6] and keratoplasty surgery^[7]. However, the intraoperative characteristics of DisCoVisc have not been reported.

In this study, we present two cases with an ink-like staining appearance and anterior subcapsular vacuolar changes in the crystalline lens that developed after DisCoVisc exposure during persistent pupillary membrane (PPM) removal surgery, and the lesions resolved spontaneously. To confirm and investigate the origin of the lens lesions, anterior lens capsules were obtained from cataract patients exposed to DisCoVisc during routine

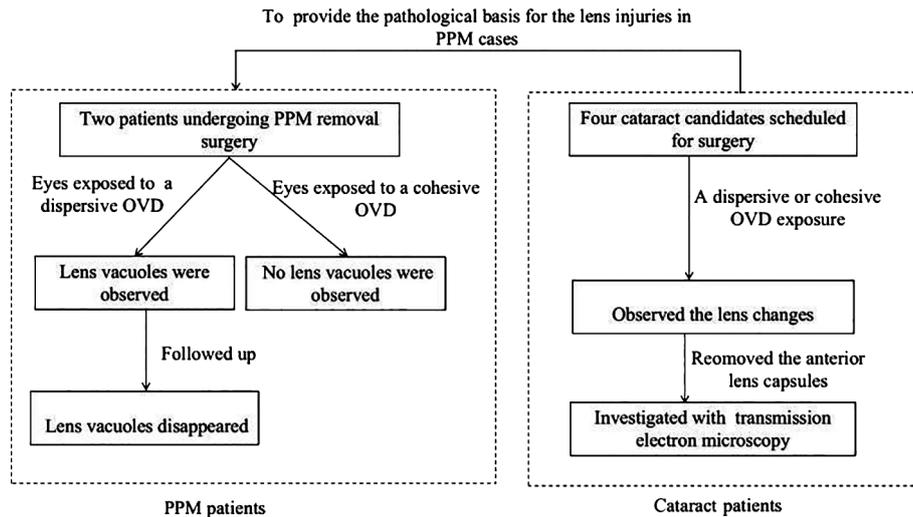


Figure 1 The flow chart of the study protocol PPM: Persistent pupillary membrane; OVD: Ophthalmic viscosurgical device.

phacoemulsification surgery for further transmission electron microscopy (TEM) examination.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Ethics Committee of the ZOC (approval number: 2020KYPJ091), Sun Yat-sen University. In accordance with the tenets of the Declaration of Helsinki, written informed consent was obtained from patients or patients' legal guardians. This is a case series study. Two patients who developed lens vacuoles after DisCoVisc exposure during PPM removal surgery were presented. Then, to further investigate the pathologic changes of the lens lesions, another four cataract patients without concomitant ocular or systemic disorders were randomly exposed to different OVDs [two patients to a cohesive OVD IVIZ (sodium hyaluronate gel 1.0%); two patients to DisCoVisc] during routine phacoemulsification surgery, and anterior lens capsules were obtained for TEM examination. The flow chart of the study protocol was shown in Figure 1.

RESULTS

Case Presentation

Case 1 A 5-year-old male presented at our outpatient department with complaints of blurred vision. Preoperatively, the best-corrected visual acuity (BCVA) was 0.4 logarithm of the minimum angle of resolution (logMAR) in the right eye and 0.7 logMAR in the left eye. Slit-lamp examinations revealed that pupillary membranes occluded the visual axis and attached to the iris collarette in both eyes (Figures 2A, 2C). Clear crystalline lenses of both eyes could be partly seen through the incompletely covered pupillary area. B-scan ultrasonography was unremarkable. Thus, a diagnosis of bilateral PPMs was established.

Bilateral pupillary membranectomy was then scheduled to be performed by an experienced ophthalmologist (Chen WR).

For the surgical procedure, after general anesthesia, a modified scleral tunnel incision was made, and an OVD was injected into the anterior chamber. The OVD then went beneath the iris strands to lift the pupillary membranes. Then, the strands were cut at the collarette uneventfully. After complete pupillary membrane removal, the OVD was carefully removed by an irrigation/aspiration probe. Finally, the scleral tunnel incision was sutured.

For the right eye, due to the careless OVD unpackage by the roving nurse, IVIZ was applied as usually used in adult cataract patients. Given that DisCoVisc is optimal but IVIZ is not forbidden for pediatric eyes, we did not ask for an OVD change. The surgical procedures were performed successfully without intraoperative complications (Figure 2B). For the left eye, we tried to use a dispersive OVD DisCoVisc to avoid viscoelastic agent retention. Surprisingly, an ink-like staining appearance and subcapsular vacuoles of the lens were observed after OVD removal (Figure 2D). For vacuolar lesions, intraoperative optical coherence tomography (OPMI Lumera 700 and RESCAN 700; Carl Zeiss Meditec AG) showed several bleb-like areas without a reflected signal beneath the anterior capsule (Figure 2E).

On the first postoperative day, the BCVA was 0.4 logMAR in the right eye and 0.7 logMAR in the left eye. Additionally, the intraocular pressure (IOP) was normal, with values of 18 mm Hg in the right eye and 17 mm Hg in the left eye. Under slit-lamp examination, both lenses were transparent with some residual pigment particles on the surface of the anterior capsule and some subcapsular vacuoles in the left lens (Figure 2F). During postoperative follow-ups, the size, and the number of the lens vacuoles in the left eye spontaneously decreased (Figure 2G–2I). Moreover, the BCVA remained 0.7 logMAR.

Case 2 A 9-year-old female presented at our outpatient department with complaints of blurred vision. Preoperatively,

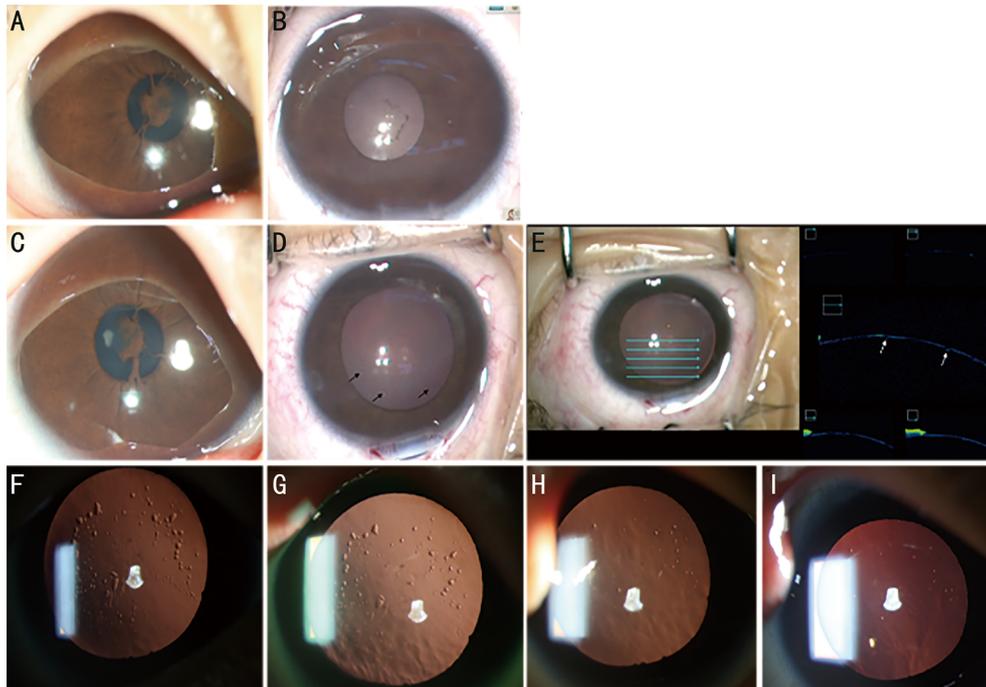


Figure 2 Anterior segment observations of Case 1 Right eye (A, B): the visual axis was preoperatively occluded by pupillary membranes (A), and some pigment particles were left after pupillary membrane removal (B). Left eye (C–I): the visual axis was preoperatively occluded by pupillary membranes (C); the ink-like staining appearance and subcapsular vacuolar changes of the lens (black arrows) occurring after DisCoVisc (hyaluronic acid 1.6%-chondroitin sulfate 4.0%) removal were observed (D); in the vacuolar lesions, the intraoperative optical coherence tomography showed several bleb-like areas without a reflected signal beneath the anterior capsule (white arrows; E); subcapsular lens vacuoles gradually disappeared at 1d (F), 1wk (G), 1mo (H), and 5mo (I) post-operation.

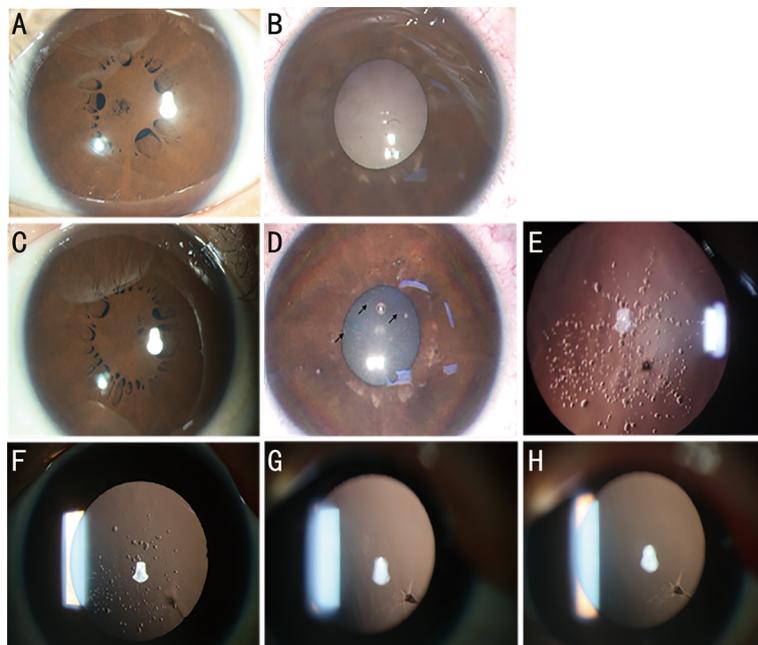


Figure 3 Anterior segment observations of Case 2 Left eye (A, B): nearly the whole pupillary area was preoperatively occluded by pupillary membranes (A), and a few pigment particles were left after pupillary membrane removal (B). Right eye (C–H): nearly the whole pupillary area was preoperatively occluded by pupillary membranes (C); the ink-like staining appearance and subcapsular vacuolar changes of the lens (black arrows) occurring after DisCoVisc (hyaluronic acid 1.6%-chondroitin sulfate 4.0%) removal were observed (D); subcapsular lens vacuoles gradually disappeared at 1d (E), 1wk (F), 1mo (G), and 5mo (H) post-operation.

the BCVA was 0.8 logMAR in the right eye and 0.2 logMAR in the left eye. Slit-lamp examinations revealed that thick

and dense pupillary membranes occluded nearly the whole pupillary area (Figures 3A, 3C). The lenses of both eyes

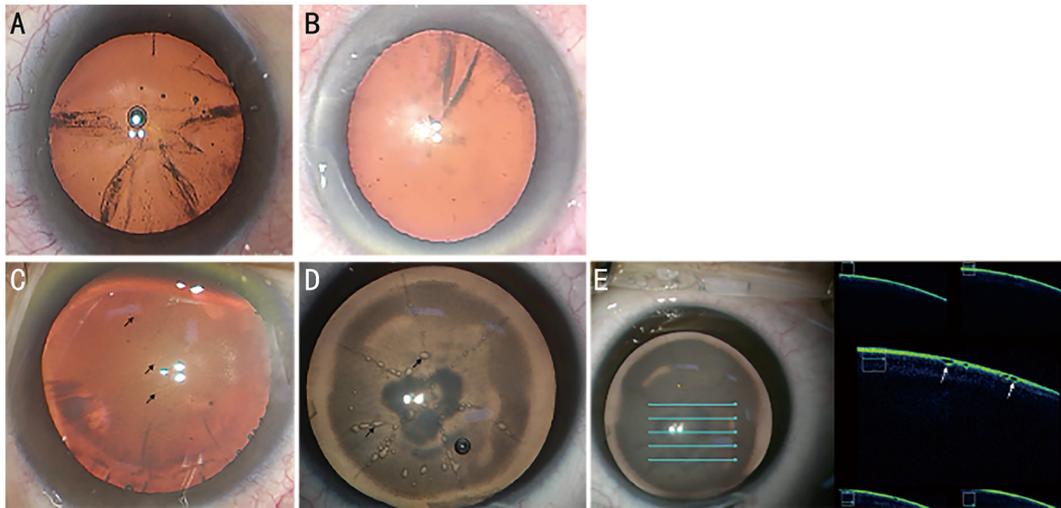


Figure 4 Anterior segment observations of the four cataract patients after intraoperative ophthalmic viscosurgical device removal. Patients 1 (A) and 2 (B): no special features were observed after IVIZ (sodium hyaluronate gel 1.0%) removal. Patients 3 (C) and 4 (D): the ink-like staining appearance and subcapsular vacuolar changes of the lens (black arrows) were observed after DisCoVisc (1.6% hyaluronic acid-4.0% chondroitin sulfate) removal. The intraoperative optical coherence tomography showed several bleb-like areas without a reflected signal beneath the anterior capsule (white arrows) in Patient 4 (E).

could not be evaluated due to the occlusion of the thick and dense pupillary membranes. B-scan ultrasonography was unremarkable. Thus, bilateral PPMs were preliminarily diagnosed.

Bilateral pupillary membranectomy was performed following the same steps as described in Case 1. As occurred in the left eye of Case 1, an ink-like staining appearance and anterior subcapsular vacuoles of the lens were also observed in the right eye with intraoperative use of DisCoVisc (Figure 3D). In contrast, for the left eye treated with IVIZ, no intraoperative complications occurred, and the lens remained transparent without any injuries (Figure 3B).

On the first postoperative day, the BCVA was 0.5 logMAR in the right eye, and 0.2 logMAR in the left eye, with normal IOPs of 14 mm Hg in the right eye and 15 mm Hg in the left eye. Some subcapsular vacuoles of the right lens (Figure 3E) and a few residual pigment particles on the anterior capsule of the left lens were observed by slit-lamp examination. During postoperative follow-ups, the size and the number of the lens vacuoles spontaneously decreased (Figure 3F–3H). Moreover, the BCVA gradually improved from 0.5 logMAR to 0.4 logMAR.

Cataract Patients All patients underwent cataract surgery by an experienced ophthalmologist (Chen WR) following the same surgical procedures. Briefly, after a corneal incision was made, an OVD was injected into the anterior chamber to stabilize the anterior chamber. To observe the lens changes during OVD removal, the OVD was washed out with compound electrolyte intraocular irrigating solution (Shike®) by a blunt washing needle instead of a routine irrigation/aspiration probe, by which the irrigation-induced friction

drag was minimized. Then, 5.5-6.0 mm circles of the anterior central lens capsules were carefully removed and prepared for TEM examination. Finally, all intraocular lenses were uneventfully implanted into the capsular bags.

During the cataract surgery, an ink-like staining appearance and anterior subcapsular vacuoles of the lens similar to the PPM cases were also presented after OVD removal in patients using DisCoVisc (Figure 4C, 4D) but not IVIZ (Figure 4A, 4B). In the corresponding lesions, intraoperative optical coherence tomography showed several bleb-like areas without reflected signals beneath the anterior lens capsule (Figure 4E).

In the TEM examination, the basement membranes of all the anterior lens capsules were homogenous and tightly connected with the cuboidal lens epithelial cells (LECs). For patients exposed to IVIZ, the LECs were arranged in a single layer with some small cytoplasmic vacuoles and tight intercellular connections (Figure 5A, 5B). For patients exposed to DisCoVisc, the LECs retained a single-layer structure but with chromatin condensation, extensive cytoplasmic vacuoles, and obvious intercellular space (Figure 5C, 5D).

DISCUSSION

DisCoVisc is a dispersive OVD with features of both cohesive and dispersive OVDs, and has been widely used in multiple ophthalmic surgeries. So far, rare complications, such as intraoperative thermal effects and postoperative floater symptoms, have been reported^[8-9]. Because OVDs are transparent tools yet very important during surgical procedures, it is essential to understand their behavior during surgery to achieve good performance. This current study reported transient ink-like staining appearances and anterior subcapsular vacuoles of the crystalline lens in patients using DisCoVisc

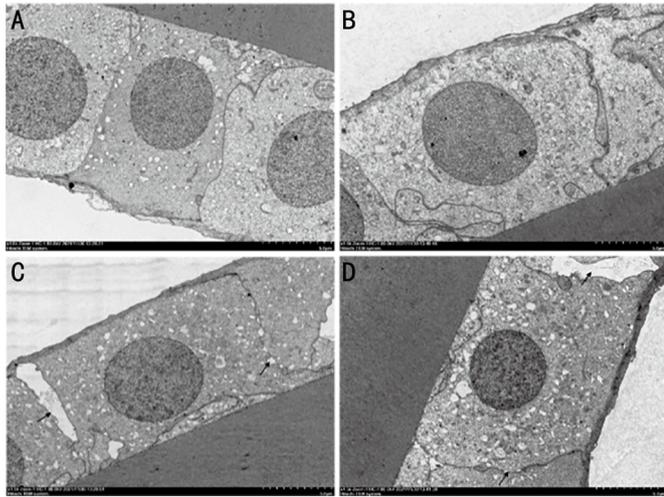


Figure 5 Transmission electron microscopy observations of the anterior lens capsule from cataract patients Patients 1 (A) and 2 (B): only a few small cytoplasmic vacuoles and tight intercellular connections were observed in the anterior lens capsule exposed to IVIZ (sodium hyaluronate gel 1.0%). Patients 3 (C) and 4 (D): chromatin condensation, extensive cytoplasmic vacuoles and obvious intercellular spaces (black arrows) were observed in the anterior lens capsule exposed to DisCoVisc (hyaluronic acid 1.6%-chondroitin sulfate 4.0%).

and provided relevant pathological evidence.

In our current study, the lenses of the cases exposed to DisCoVisc developed subcapsular vacuoles, whereas no similar lesions occurred in the contralateral lenses exposed to IVIZ. Similar lens changes were also reported by Gros-Otero *et al*^[10]. A myopic patient developed lens vacuoles during implantable collamer lens replacement with intraoperative use of a dispersive OVD Viscoat (sodium hyaluronate 3% and chondroitin sulfate 4%). Consistent with Gros-Otero *et al*^[10], we speculated that the DisCoVisc/Viscoat might be associated with the observed appearance of the lens vacuoles. The shared properties of the dispersive OVDs might contribute to the observed lens injuries. In addition, Chung *et al*^[11] also reported similar lens vacuoles in 2 myopic patients undergoing implantable collamer lens implantation with the intraoperative use of DisCoVisc. They believed that the friction drag on the lens capsular surface during the irrigation procedure was responsible for the lens injuries. However, DisCoVisc could be considered another cause of the lesions because of its different physical and chemical properties from the cohesive OVDs recommended by STAAR Surgical. In our selected cataract patients, despite gently removing the OVDs by a blunt washing needle instead of the irrigation procedure, subcapsular vacuolar lesions of the lenses were still observed. This finding rules out the possibility of irrigation-induced friction drag.

The anterior lens capsule is composed of the basal lamina and a single layer of cuboidal cells, which plays an important

role in maintaining lens transparency^[12]. Any systemic and topical factors disturbing the morphology of the lens capsule would lead to lens injuries. In recent years, several cases of lens injuries caused by uncontrolled acute hyperglycemia^[13-14], ocular trauma^[15-16], yttrium aluminum garnet laser iridotomy^[17] and distilled water^[18] were reported to be reversible. Among them, most cases were presented with posterior subcapsular cataract, which was commonly caused by disturbances of the ion pump or abnormality of the metabolic enzyme activity^[19]. In addition, Yang *et al*^[18] reported a reversible anterior subcapsular cataract caused by mistakenly infusing distilled water into the anterior chamber during astigmatic keratotomy. In their case, thin vacuolar anterior subcapsular opacity was observed on the first postoperative day and gradually decreased during the follow-ups. It was speculated that the transient permeability changes caused by the instantaneous exposure to distilled water should be responsible for the reversible lens injuries^[18]. In the present study, the anterior lens capsules exposed to DisCoVisc had larger intercellular spaces between LECs and more extensive cytoplasmic vacuoles in LECs. Although the mechanism cannot be clearly explained, we speculate that certain properties of DisCoVisc might damage the cellular junction, induce an increase in paracellular permeability, and lead to the intraoperatively observed subcapsular vacuoles. Since the repair potential of LECs could be activated in certain microenvironments^[20-21], we believe that the lens vacuoles in our cases gradually disappeared with the recovery of LECs.

Limitations and Recommendations When interpreting this study, the following two limitations should be considered. First, since the anterior capsules of the PPM patients were unavailable due to the perseveration of the injured lens, the anterior capsules of cataract patients exposed to OVDs were obtained for TEM instead, which can not entirely reflect the pathological changes of the lens in PPM cases. Second, the lens capsules might be traumatized by surgical instruments during the surgery. However, all cataract patients underwent cataract surgery by the same experienced ophthalmologist; therefore, we believe that the possible damage in the lens capsules is minimized and comparable among cataract patients. Third, since the sample size of the current study is limited, further relevant studies including more cases are still warranted to verify our findings.

Despite the limitations in this current study, to our knowledge, this was the first study to report transient lens vacuoles possibly related to DisCoVisc exposure and provide the corresponding pathological findings. To avoid this event, a meticulous selection of OVDs is required during OVD injection, and dispersive OVDs should be cautiously used in patients with transparent lenses or without the intention of lens

extraction. Furthermore, because of the reversibility of the lens injuries, close follow-ups instead of immediate intervention, such as lens extraction, are recommended once a similar event occurs.

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